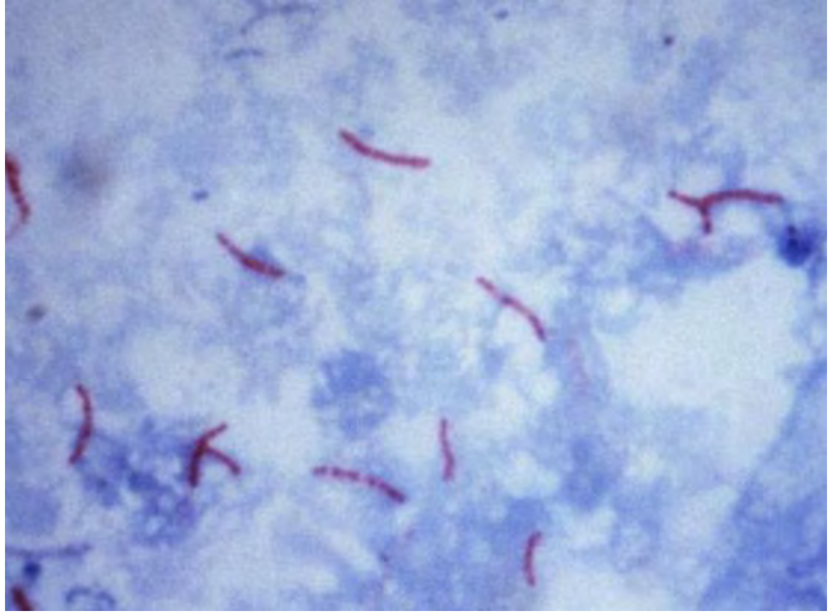


Tuberculosis

The Great White Plague Keeps Coming Back

Demystifying Medicine

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Tuberculosis Research Section
National Institute of Allergy and Infectious Diseases
National Institutes of Health
January 22, 2019

Case Scenario 1

35 year old homeless male presents with cough x2 months that has gradually gotten worse. Patient's cough is productive of yellow phlegm and has persisted despite OTC cough remedies. His phlegm has occasionally been blood-tinged recently. He also reports intermittent fevers and sweats and feeling poorly overall. He says this cold is worse than his usual colds and he hasn't been able to get over it. He has lost weight over the last few months but says this is due to not having consistent meals. He does not feel short of breath and is able to continue working during the day selling newspapers. He has otherwise been relatively healthy and does not take any regular medicines. He has smoked for 20 years but does not drink or do drugs. No one else around him at the shelter has been sick, that he knows of. He reports testing PPD+ last year but said the reaction was because he kept scratching at the site so declined further treatment.

Case Scenario 1

Physical exam:

- Thin AAM in no distress but with occasional cough
- Temp: 99.9^{o}F; BP 140/72; HR 104; RR 20
- Physical exam is normal, including the lung exam.

He does not look acutely ill and chronic coughs are common, especially in smokers. What do you do next?

A. This is probably a smoker's cough. Give him Robitussin and have him follow-up in 1-2 weeks for further evaluation if not better.
B. This is more likely a viral or bacterial upper respiratory infection. Give him a Z-pack and have him follow-up in 1-2 weeks for further evaluation if not better.
C. This is concerning for TB or other more serious diseases. Order a CXR now.

Case Scenario 1

This CXR is very concerning for active TB. You send a sputum sample to the lab for AFB smear and culture. What do you do next?

A. Since he is not acutely ill, start empiric TB therapy as an outpatient.
B. Admit him to the hospital for evaluation and empiric TB therapy.

Case Scenario 2

33 year old Asian female is a researcher who came to the US two years ago for a post-doctoral research program. Her mother was treated for TB when she was very young. The patient was also treated for TB about 10 years ago for about 9 months. She has been well since. Over the past few months, she developed a cough with bloody phlegm, low grade fevers, shortness of breath, and fatigue. She was initially admitted to an outside hospital, where she was diagnosed with TB and discharged on standard therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. One month later, drug sensitivity testing results show resistance to isoniazid and rifampin, as well as the fluoroquinolones and aminoglycosides. What are your treatment options now?

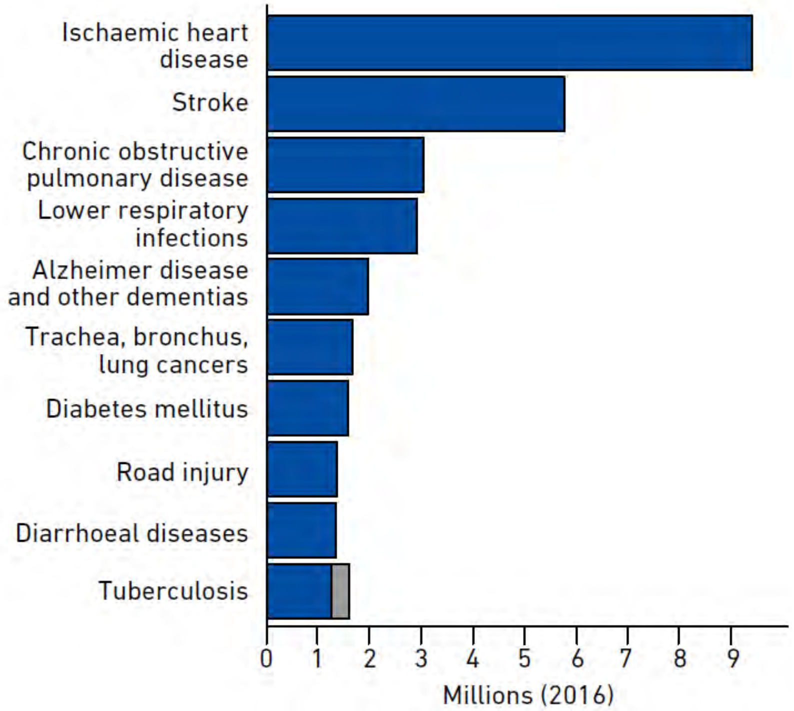
Overview

- Global and US TB epidemiology
- Latent TB
- Active TB and drug resistance
- Recent studies advancing our understanding of TB treatment
- New drugs and how to apply them
- Conclusions

Tuberculosis – Why should we care in 2019?

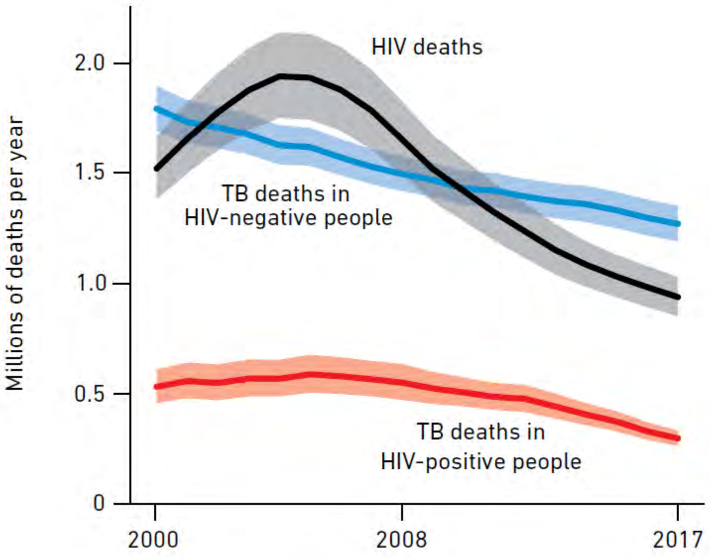
- 10th leading cause of death globally

FIG. 3.11
Top causes of death worldwide in 2016.[a,b]
Deaths from TB among HIV-positive people are shown in grey.



- Leading cause of death from a single infectious agent, surpassing HIV

FIG. 3.13
Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2017.[a,b]
Shaded areas represent uncertainty intervals.



WHO. Global Tuberculosis Report 2018.

Global TB Incidence and Mortality Rates

FIG. 3.4

Estimated TB incidence rates, 2017

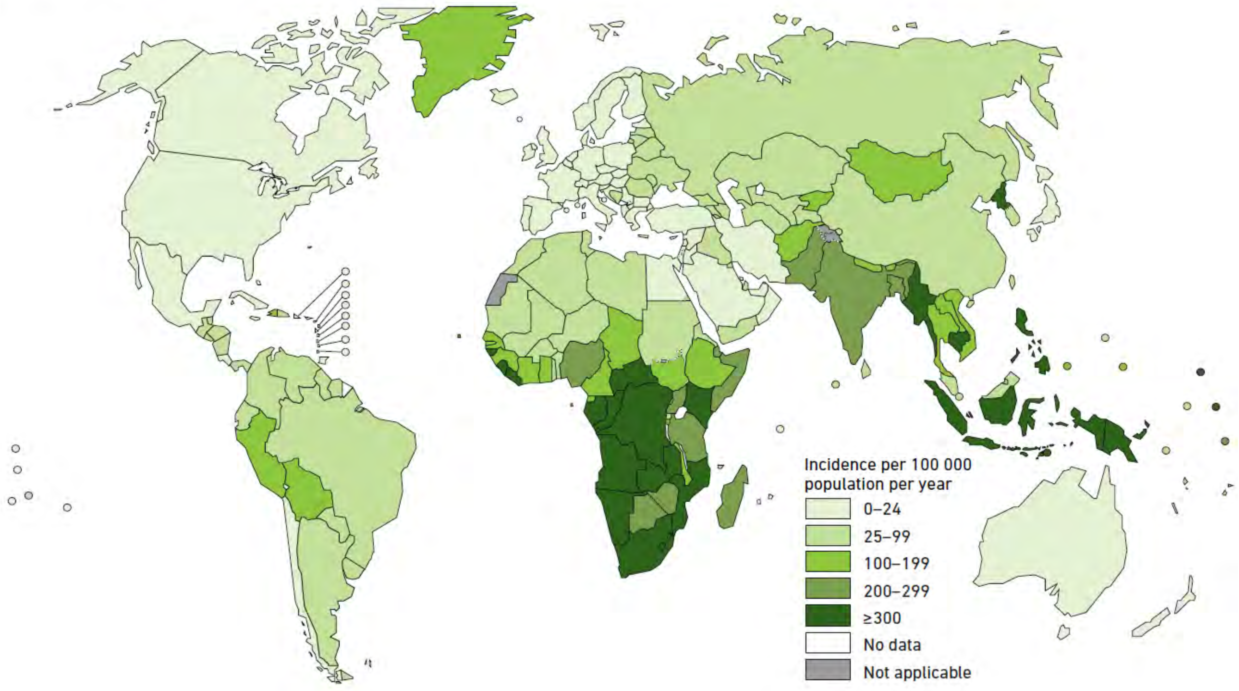
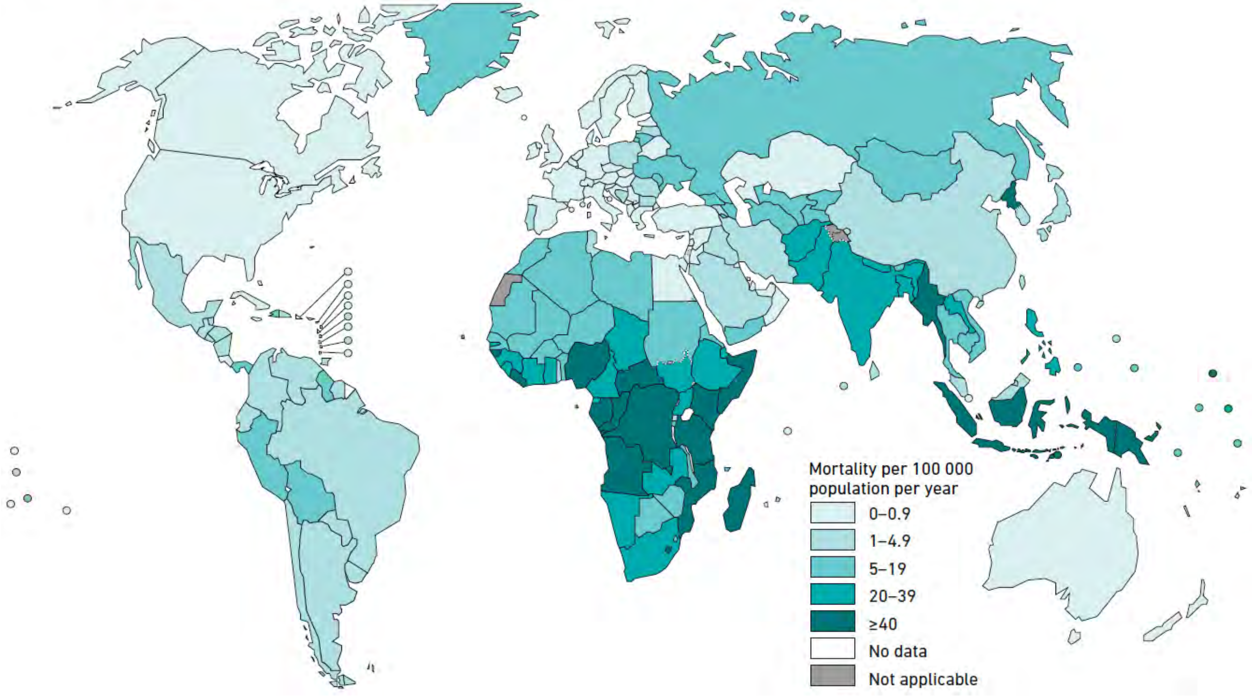


FIG. 3.14

Estimated TB mortality rates excluding TB deaths among HIV-positive people, 2017

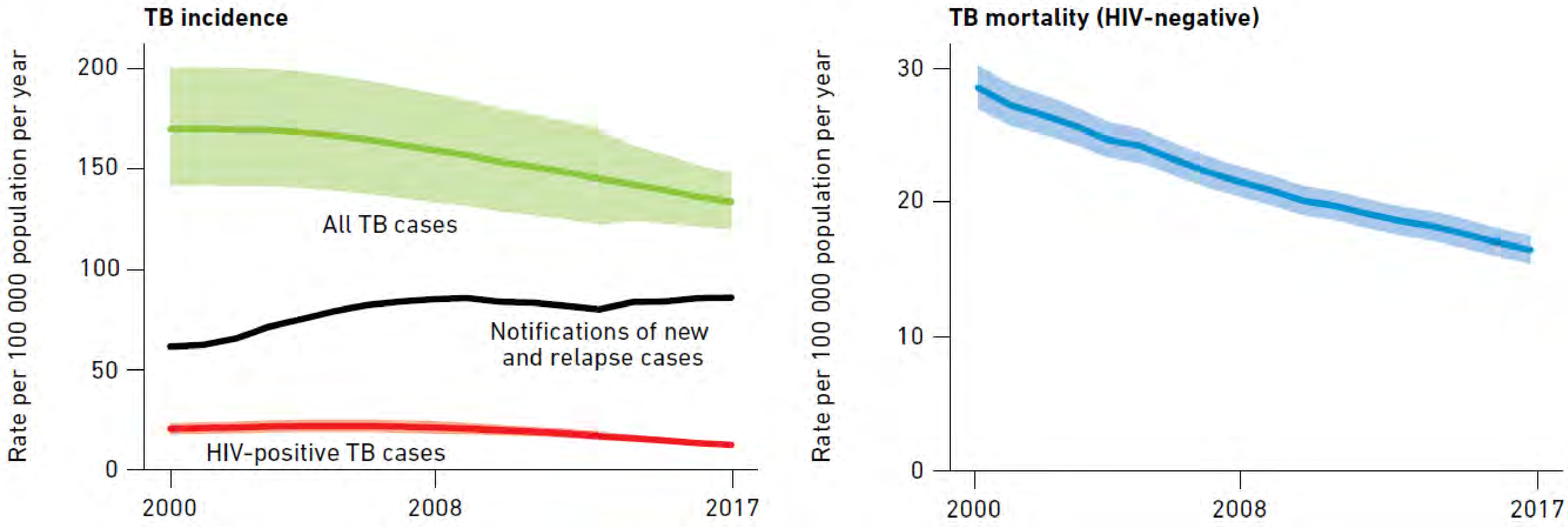


WHO. Global Tuberculosis Report 2018.

Global TB Incidence and Mortality

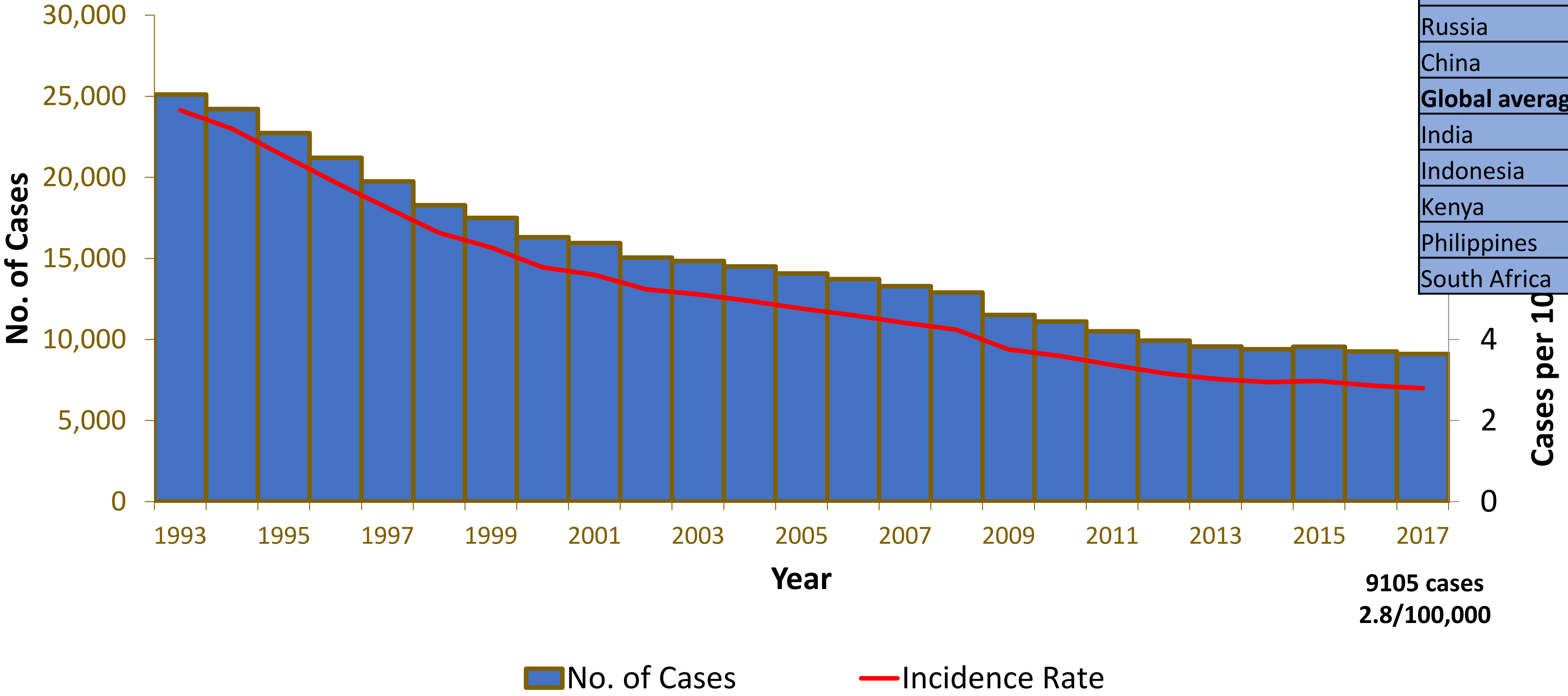
FIG. 3.7

Global trends in estimated TB incidence and mortality rates, 2000–2017. Shaded areas represent uncertainty intervals.



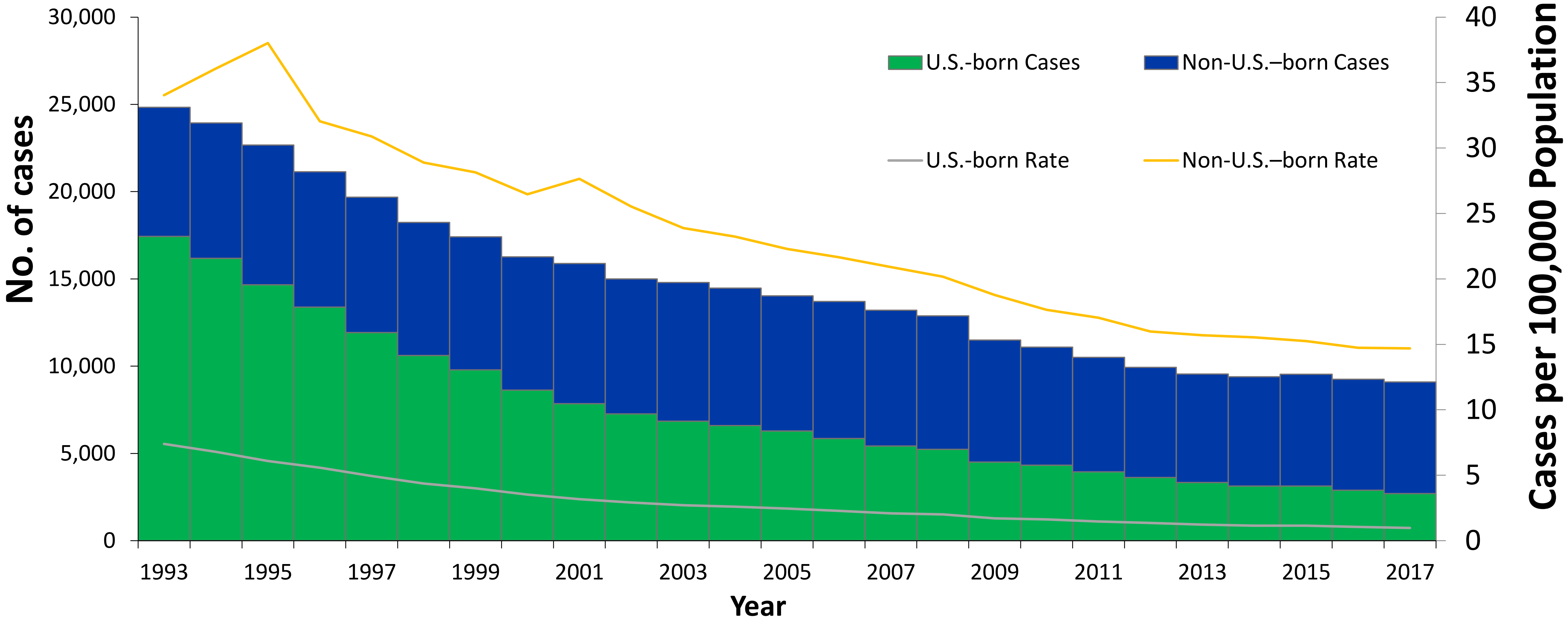
WHO. Global Tuberculosis Report 2018.

Reported Tuberculosis (TB) Cases and Rate United States, 1993–2017



Country	2017 Incidence (/100,000)
Canada	5.5
UK	8.9
Mexico	22
Brazil	44
Russia	60
China	63
Global average	**133**
India	204
Indonesia	319
Kenya	319
Philippines	554
South Africa	567

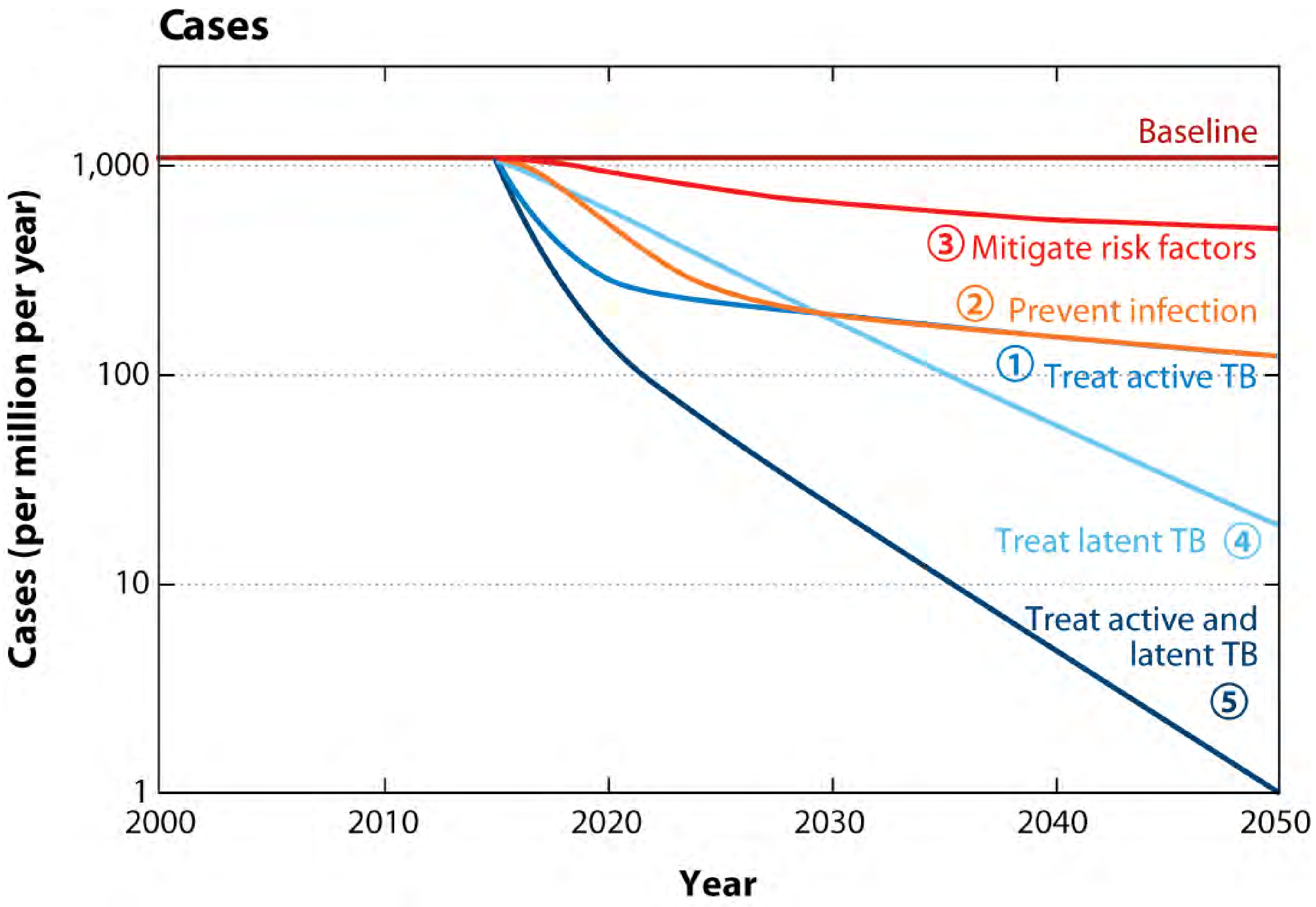
TB Cases and Rates Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2017




Active TB disease: 8 million new cases per year
TB DISEASE
LATENT TB INFECTION
-the "hidden epidemic"
-2 billion people infected

Diagnosis: Purified Protein Derivative (PPD)

- Mantoux tuberculin skin test
  - 5 tuberculin units (0.1 ml) of PPD
  - Test is not specific for *M. tb*



Dye C, et al. 2013.
Annu. Rev. Public Health. 34:271–86

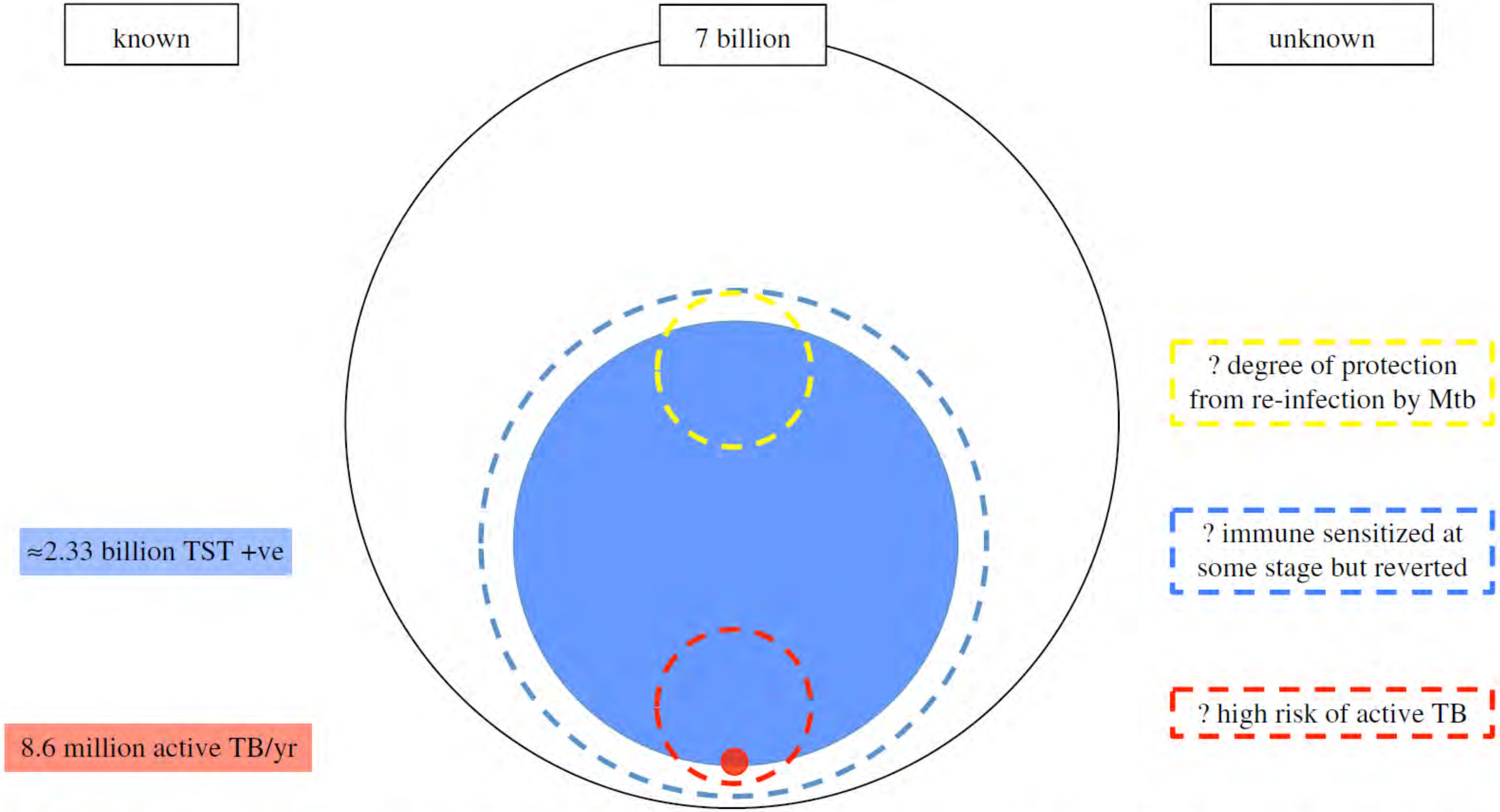


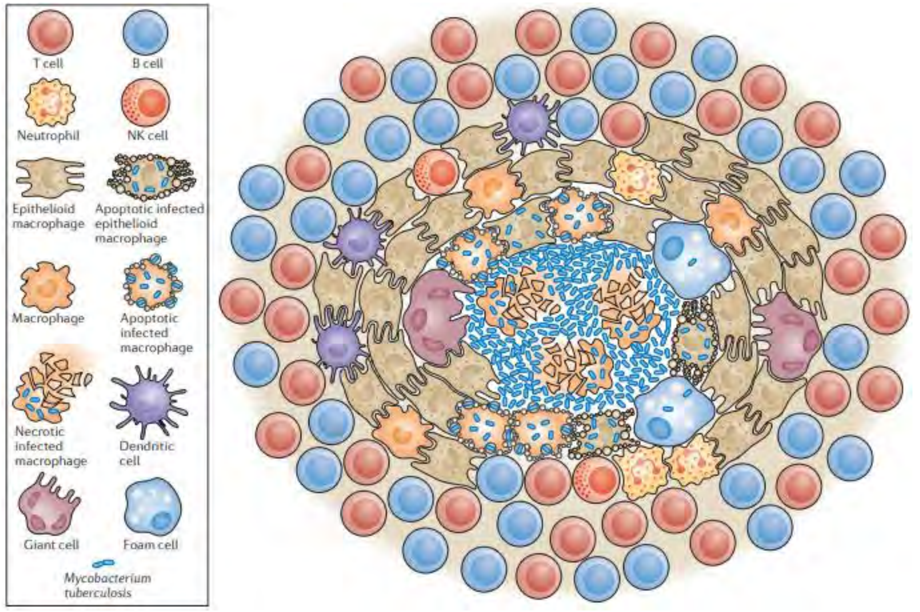
Figure 1. Reservoir of TB—we currently have estimates for proportion of population that are immune sensitized (large circle) and number of cases of active TB annually (small filled circle). As TST and IGRA reversion can occur, total number of exposed persons may be greater than this (larger dashed circle), in addition TST and IGRA are only moderately sensitive for active TB. A much smaller pool of people may be at much higher risk of TB (bottom small dashed circle) and also a proportion of people may receive considerable protection against reinfection (top small dashed circle). Identifying these additional populations may be very valuable. (Online version in colour.)

Review article: The ongoing challenge of latent tuberculosis

H. Esmail, C. E. Barry, D. B. Young, R. J. Wilkinson

Phil. Trans. R. Soc. B 2014 369 20130437; DOI: 10.1098/rstb.2013.0437. Published 12 May 2014

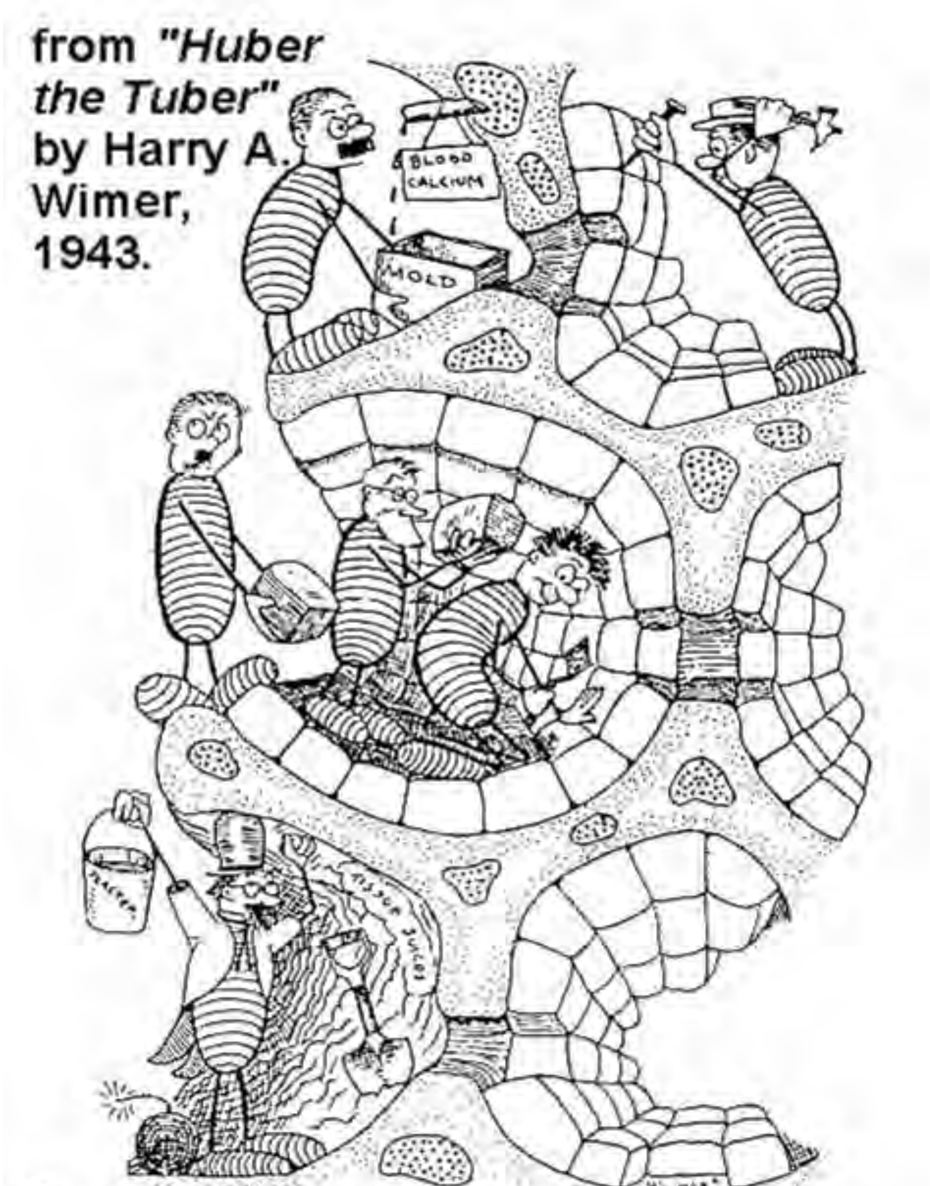
Pathogenesis



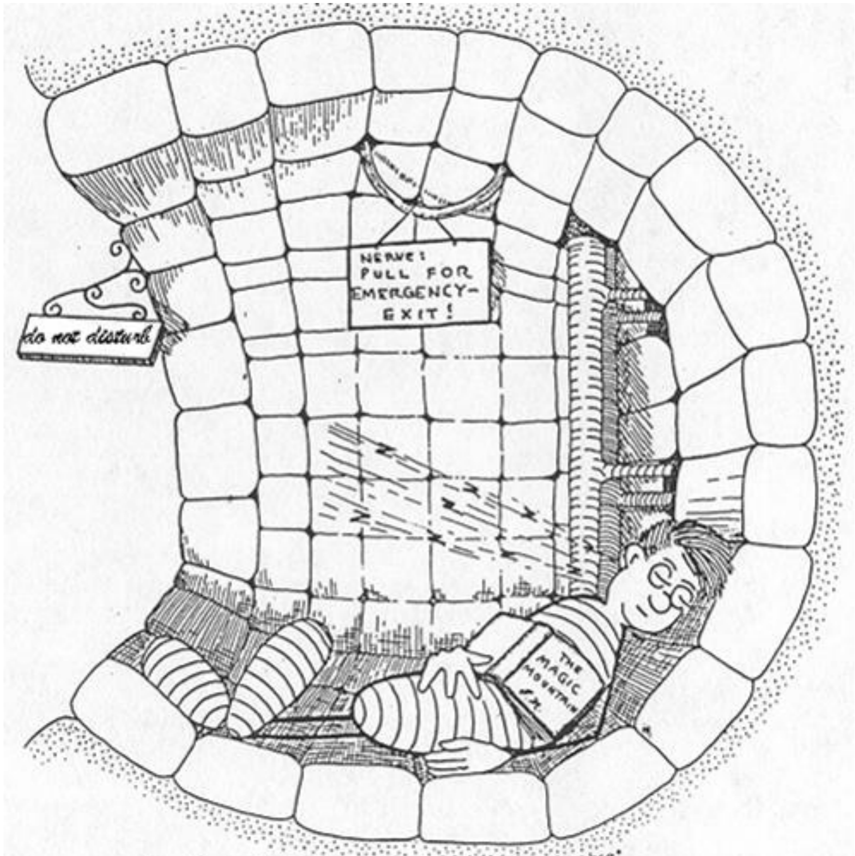
- Infection via droplet nuclei, causes granulomatous inflammatory process due to macrophages, lymphocytes, and fibroblasts recruited to site of infection
  - Bacteria in granuloma may become dormant (latent)
  - Granuloma may have caseous necrotic center
- If latently infected, about 10% lifetime risk of developing active TB
  - About 5% over initial 2 years post infection
  - About 5% over remaining lifetime
- If co-infected with untreated HIV, roughly 10% risk of TB activation/year
- Active infection may spread via bloodstream (miliary); more common in young children and immunocompromised

Ramakrishnan L. Nat Rev Immunol 2012 Apr 20;12(5):352-66.

"1/3 of the world's population is infected with latent TB"



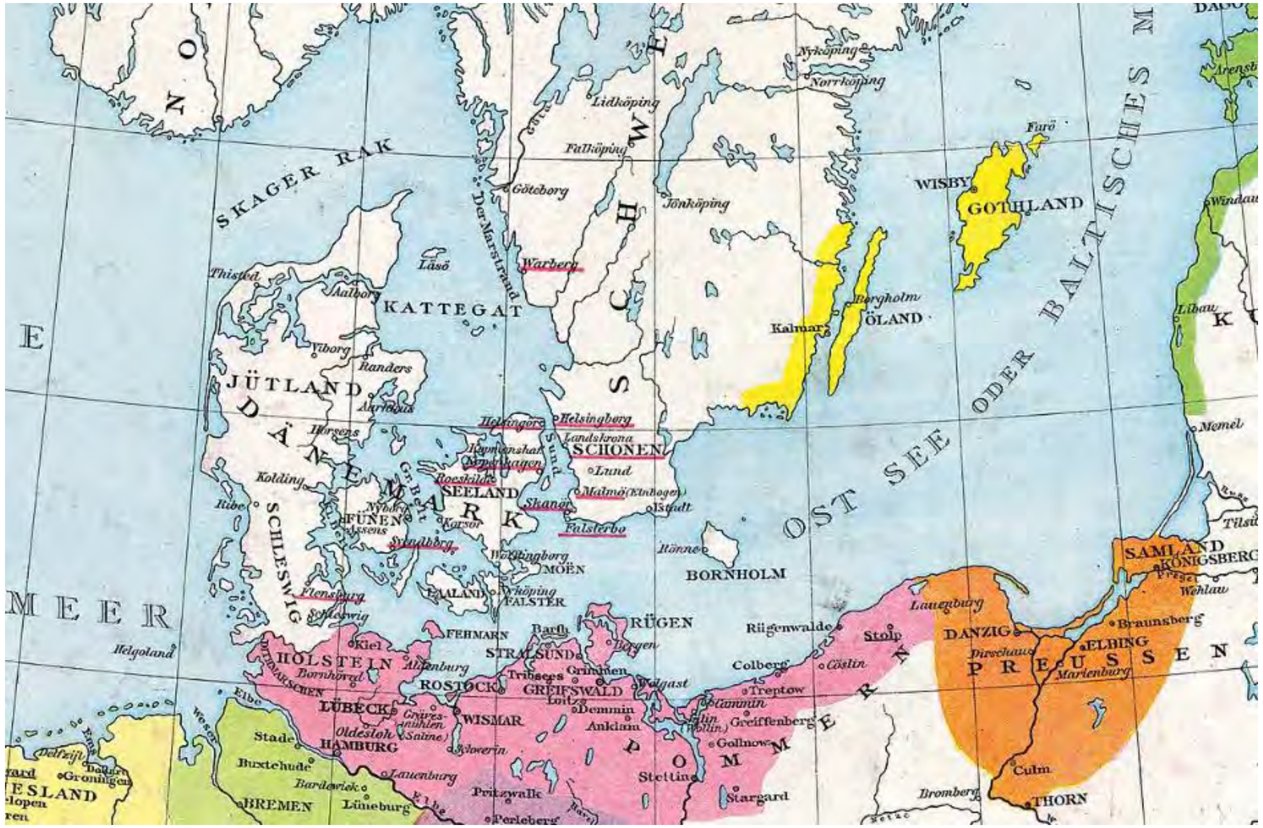
Granuloma formation, maintenance



Latent Tuberculosis

The “Lübeck Disaster”

The Lubeck disaster, 1930 "Between 10 December 1929 and 30 April 1930, 251 of 412 infants born in the old Hanseatic town of Lübeck received three doses of BCG vaccine by the mouth during the first ten days of life. Of these 251, 72 died of tuberculosis, most of them in two to five months and all but one before the end of the first year. In addition, 135 suffered from clinical tuberculosis but eventually recovered; and 44 became tuberculin-positive but remained well. "---Sir Graham Wilson (Hazards of Immunisation p66)



29% Death rate
82% Disease rate
100% Infection rate

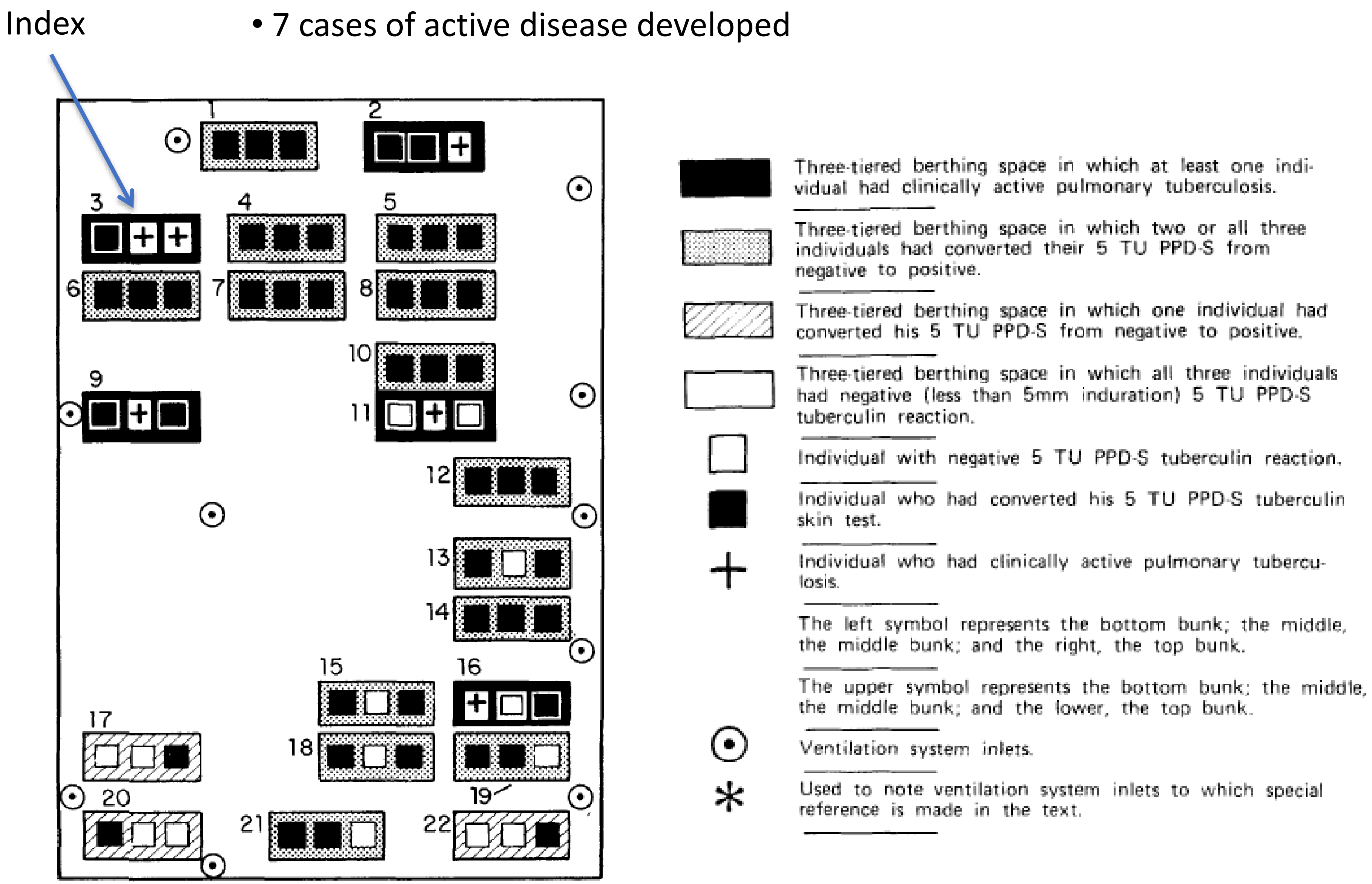
at a high enough dose disease outcomes are severe

Over a year earlier, in May, 1965, aboard the U.S.S. *Richard E. Byrd*, a Navy ship with over 350 enlisted members and officers, a seaman had converted his five tuberculin unit (TU) tuberculin skin test from negative to positive. At that time, the seaman's chest roentgenogram was normal and his medical officer elected not to place him on isoniazid chemoprophylaxis.

Ten months later, in March, 1966, the seaman began to exhibit significant symptoms. Though he attended sick call on three occasions, the illness was diagnosed as a virus infection. A chest roentgenogram was not done until late August, 1966, about six months after the appearance of the significant symptoms. At that point, a diagnosis of tuberculosis was made, and the seaman was transferred from the ship to the U.S. Naval Hospital at St. Albans, New York.

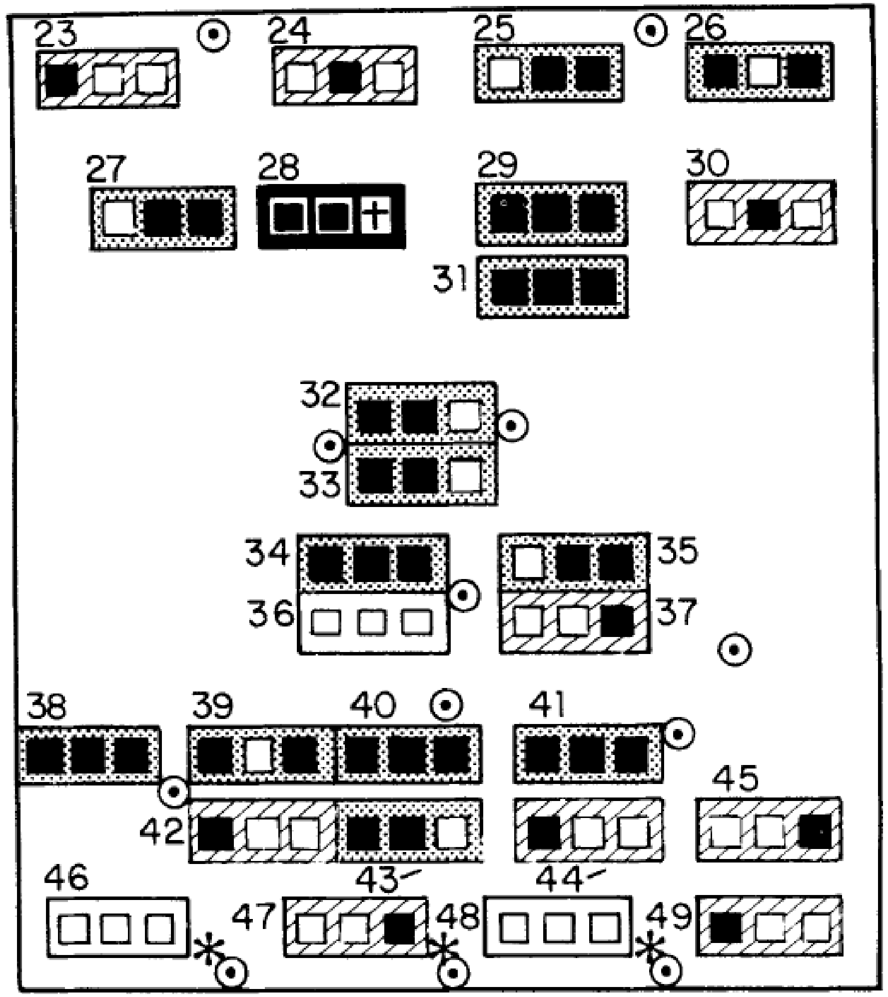
Over that six month period of exposure…

- 140 (46%) converted from known negative to positive PPD
- 7 cases of active disease developed



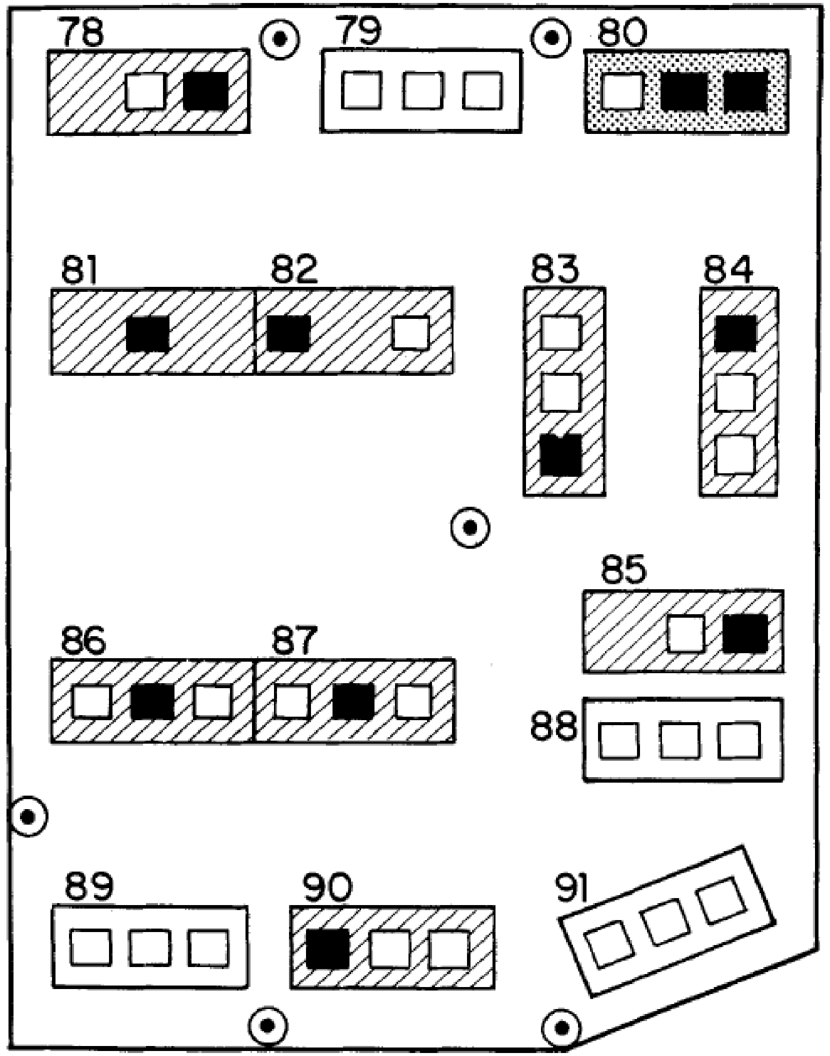
COMPARTMENT DIAGRAM 1

1. Compartment that berthed six of the seven individuals with active disease.



COMPARTMENT DIAGRAM 2

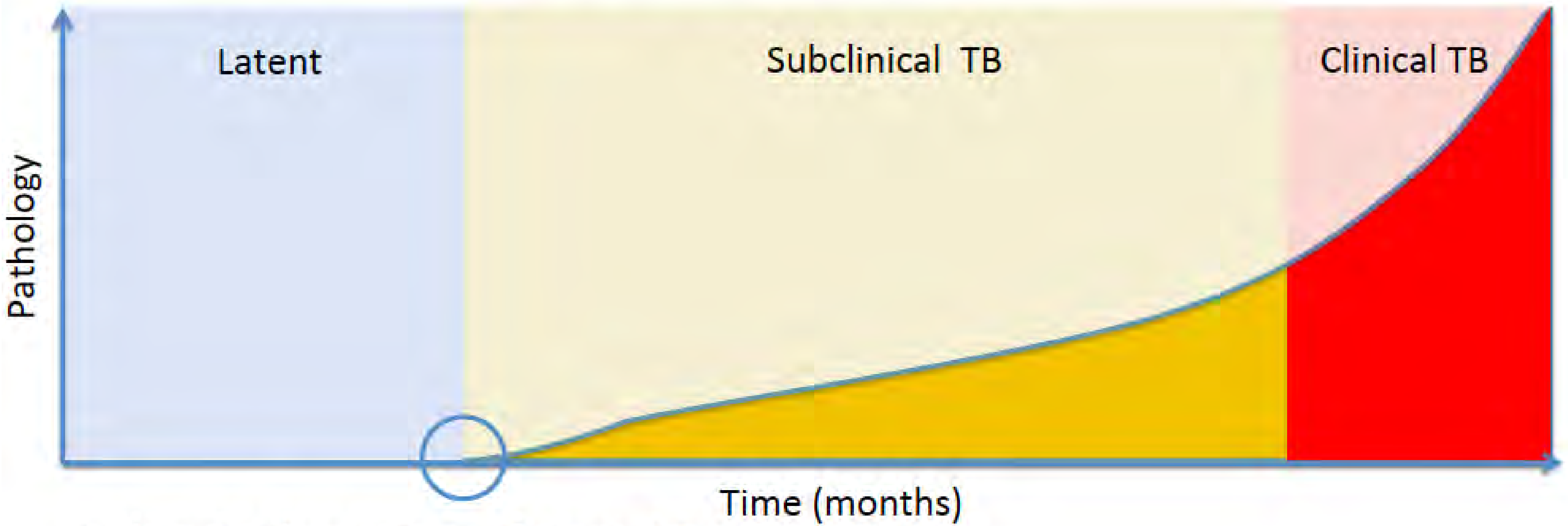
FIGURE 2. Another highly infected compartment. Ventilation comes from the same system as for Compartment One.



COMPARTMENT DIAGRAM 5

FIGURE 5. Crew's quarters for enlisted personnel in the supply division, including cooks.

Subclinical TB



What is the point of transition?

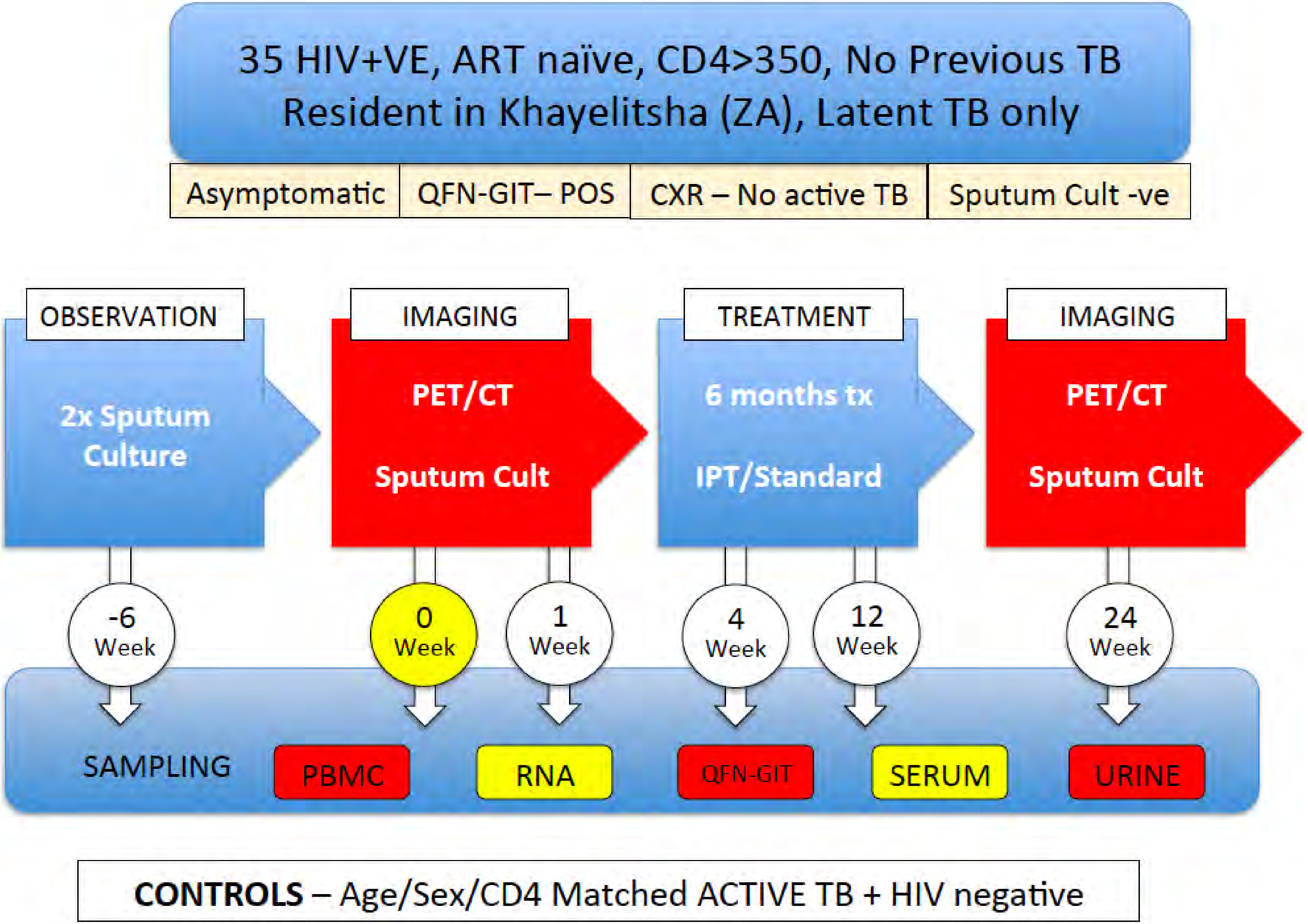
- Animal studies suggest development of TB pneumonia when proliferation exceeds "carrying capacity" of granuoma[1]
- Histo-pathological studies support development of TB pneumonia as the earliest event in active pulmonary TB[2]

[1]Lin et al, Nature Medicine 2014. [2]Hunter, Tuberculosis 2011

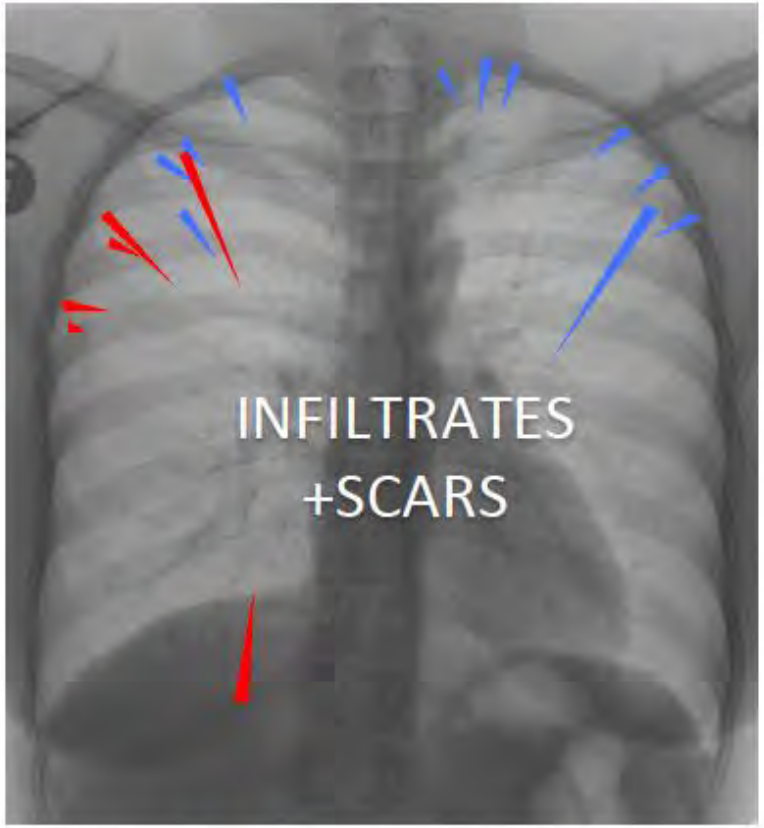
PET/CT Study UCT

- Use FDG-PET/CT to identify pathology consistent with Subclinical disease in asymptomatic HIV infected persons (CD4>350, ART naïve) with evidence of Latent TB infection (QFN-GIT)

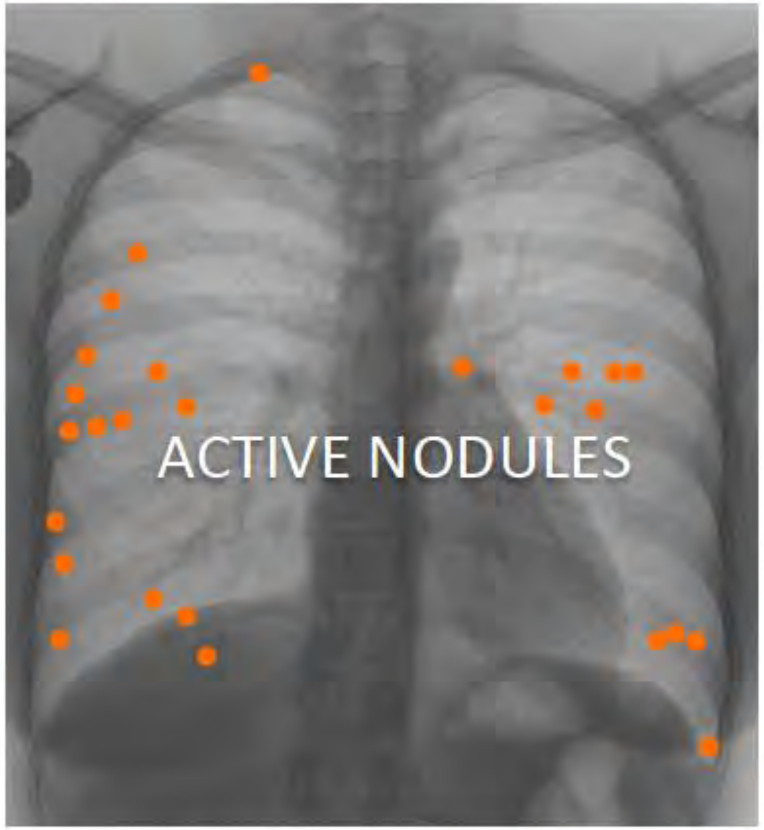
- Derive transcriptional signature and serum biomarkers for Subclinical TB disease


35 HIV+VE, ART naïve, CD4>350, No Previous TB
Resident in Khayelitsha (ZA), Latent TB only
Asymptomatic
QFN-GIT– POS
CXR – No active TB
Sputum Cult -ve
OBSERVATION
2x Sputum Culture
IMAGING
PET/CT
Sputum Cult
TREATMENT
6 months tx
IPT/Standard
IMAGING
PET/CT
Sputum Cult
-6 Week
0 Week
1 Week
4 Week
12 Week
24 Week
SAMPLING
PBMC
RNA
QFN-GIT
SERUM
URINE
CONTROLS – Age/Sex/CD4 Matched ACTIVE TB + HIV negative

2 patterns of subclinical TB on PET/CT

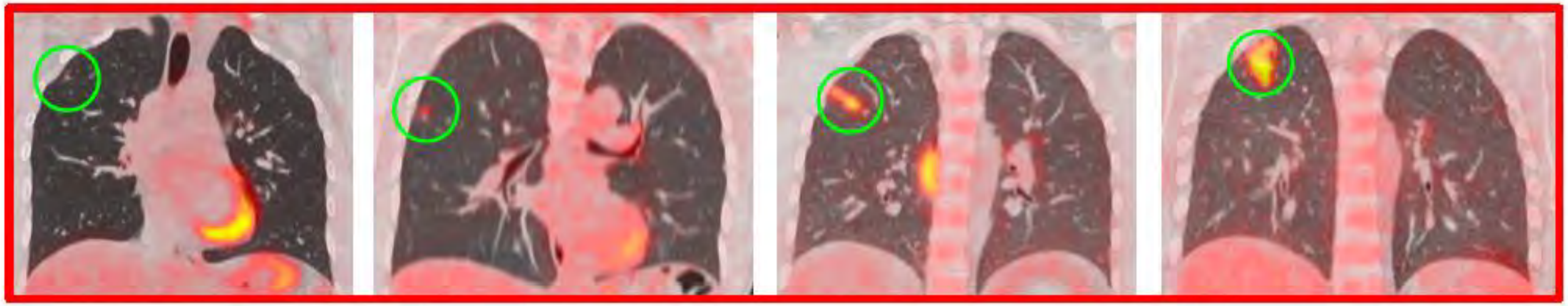


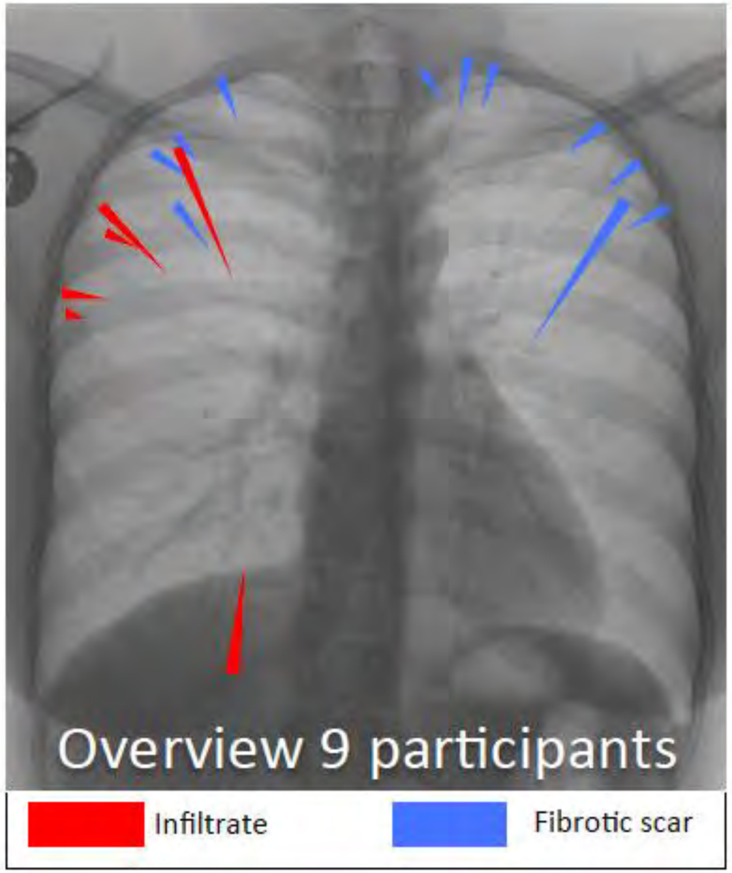
Consistent with
bronchogenic spread

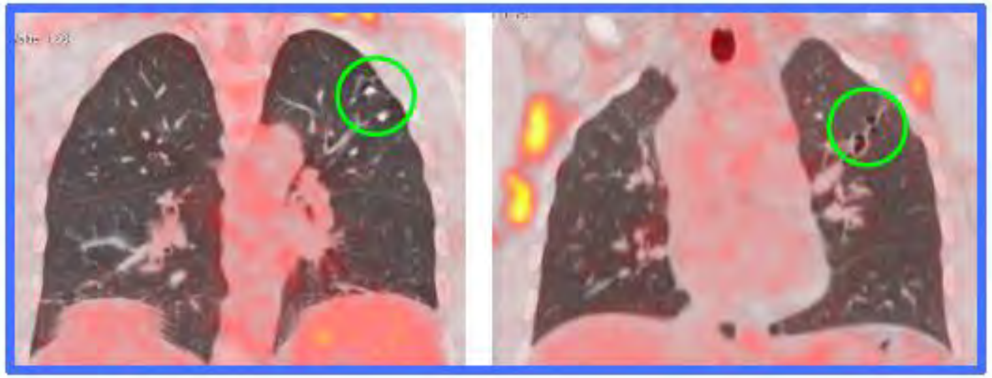


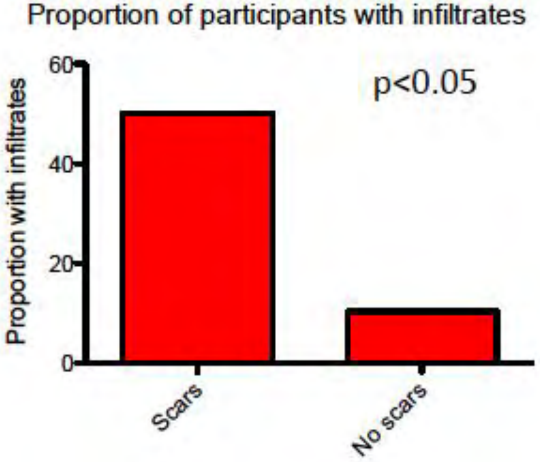
Consistent with
haemotogenous spread

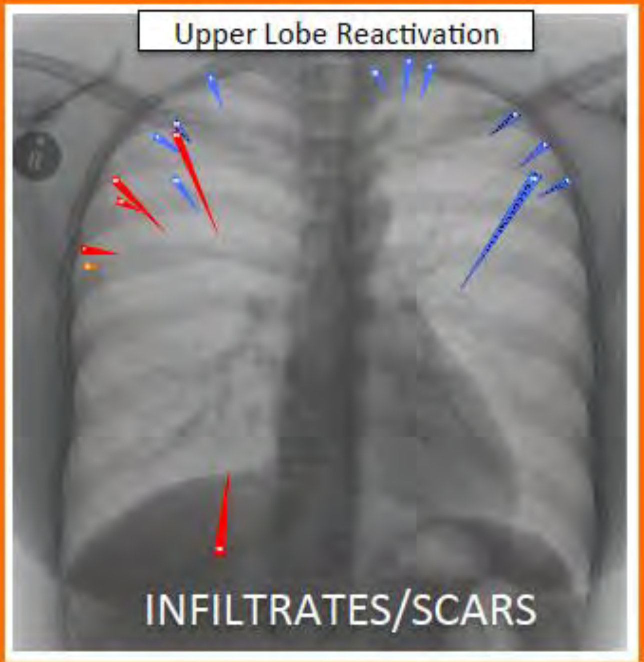
Infiltrate and Fibrotic scars

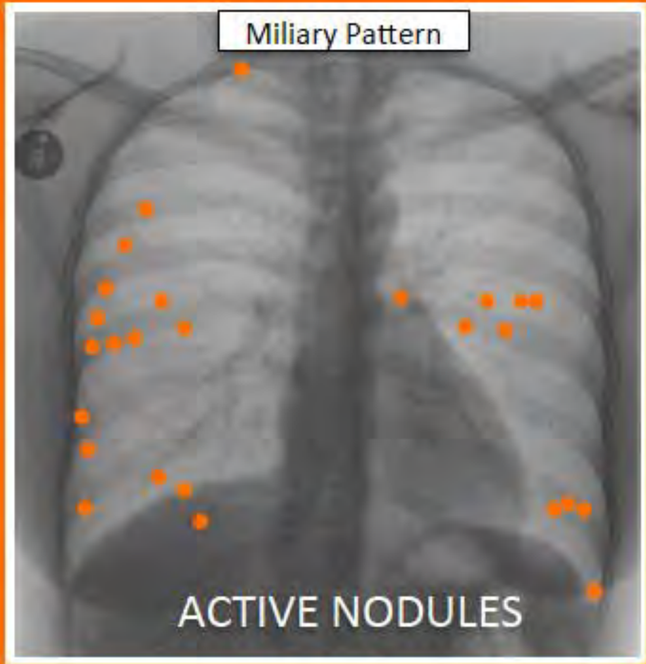




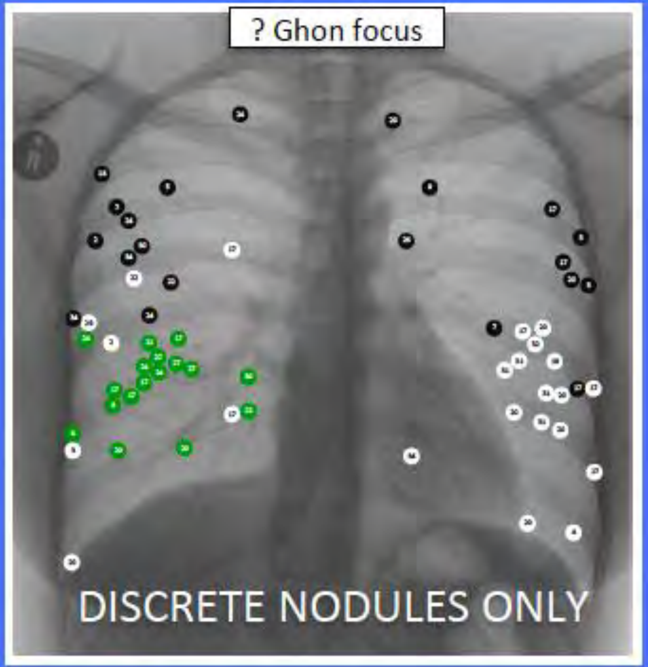


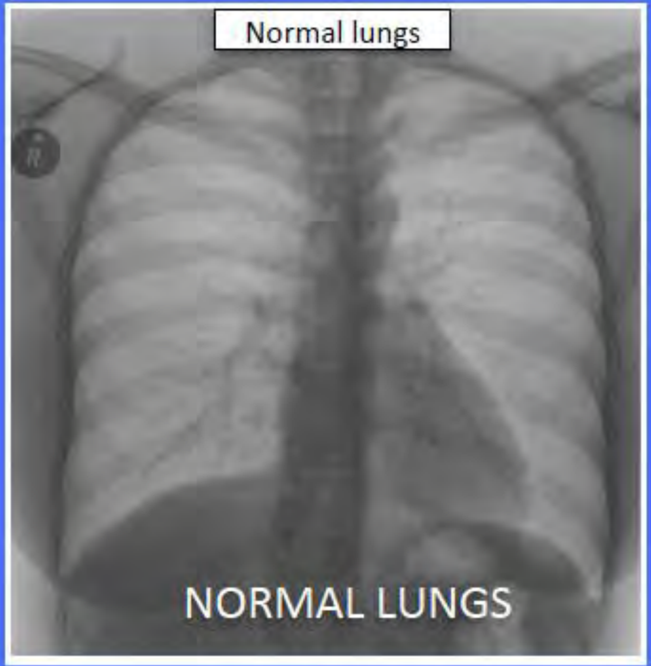






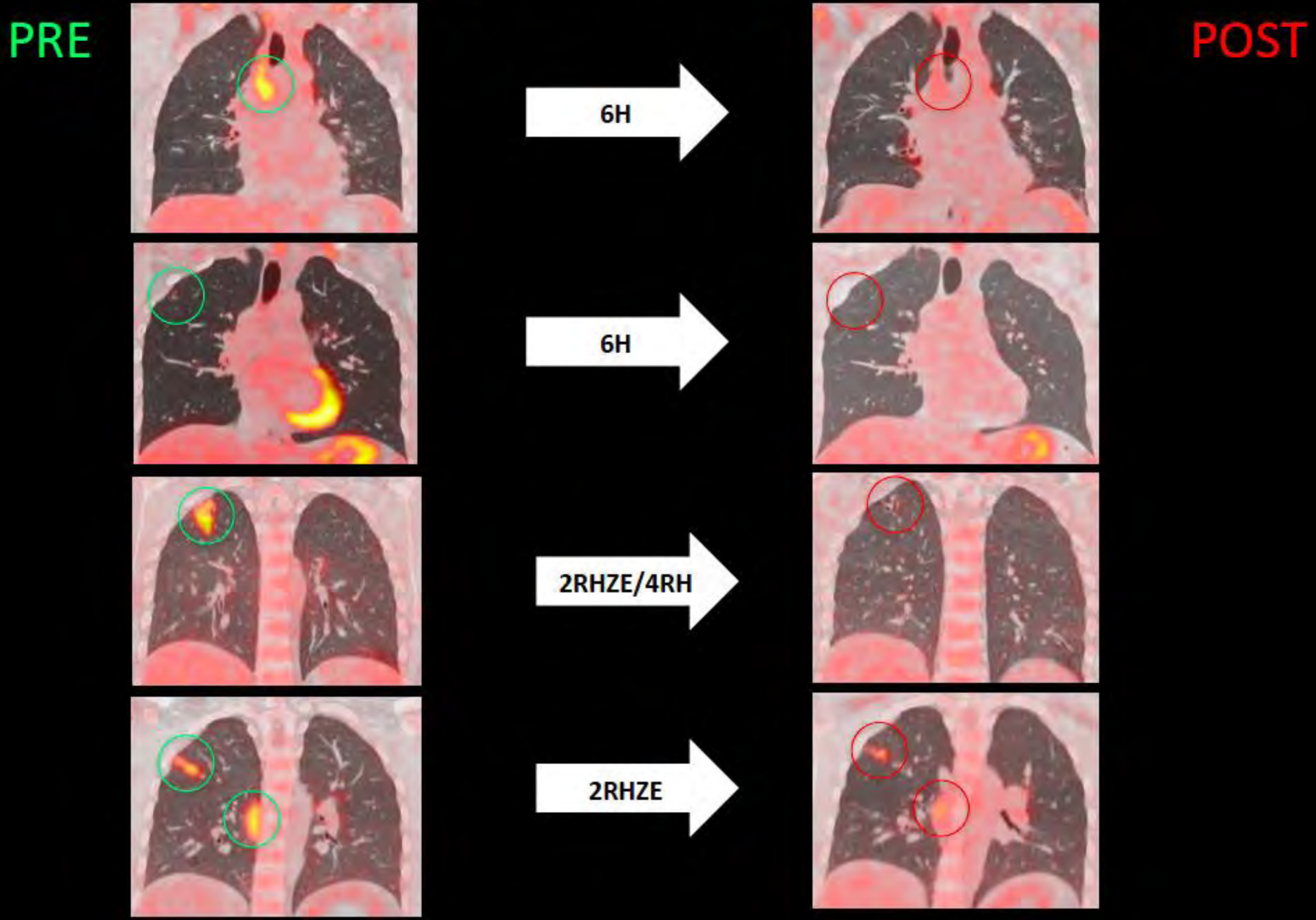
10
SUBCLINICAL





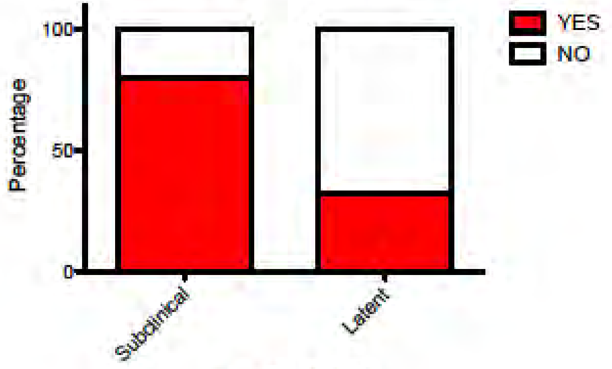
25
LATENT

Response to treatment



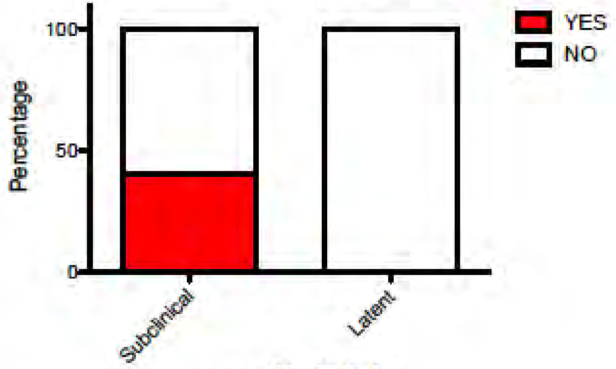
Subclinical TB

Increased FDG uptake in mediastinal LN



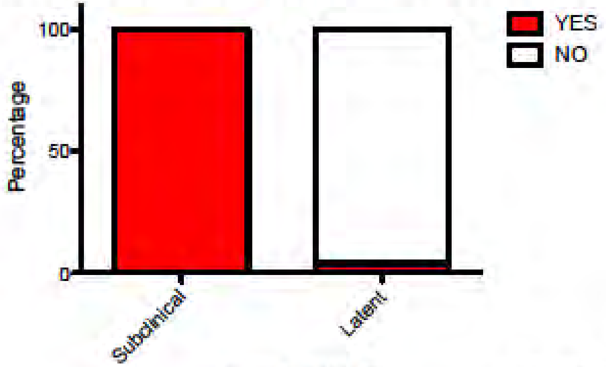
p=0.022

Microbiological/clinical evidence of active TB during follow-up

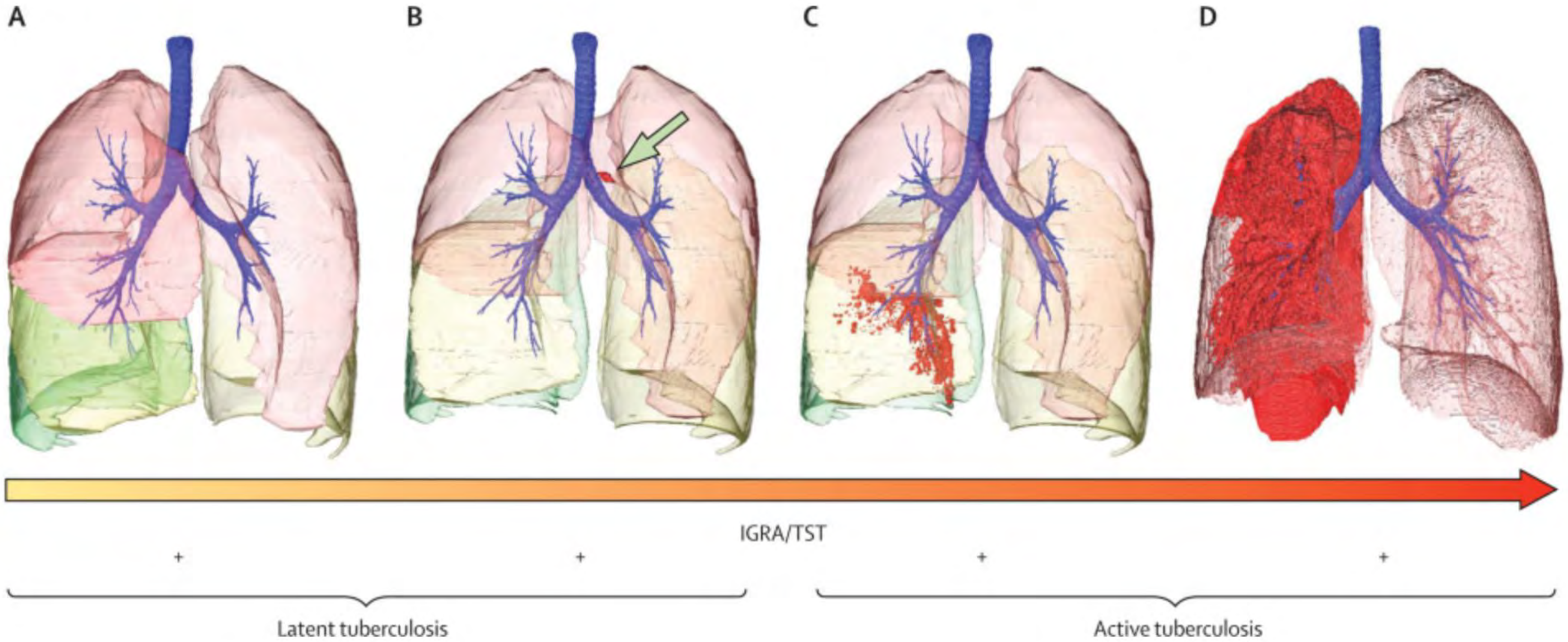


p=0.004

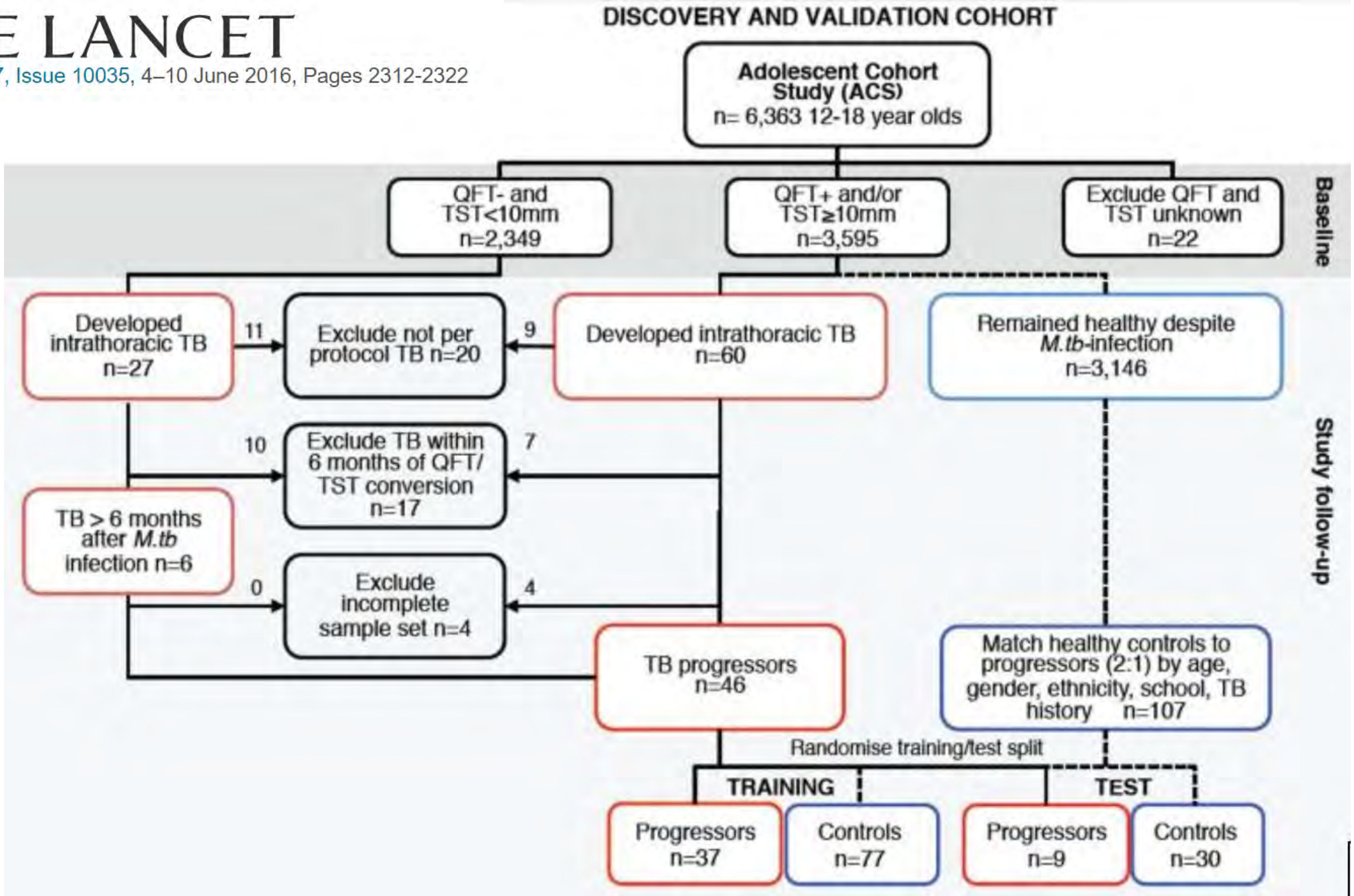
Improvement in baseline PET/CT abnormalities after 6/12 treatment

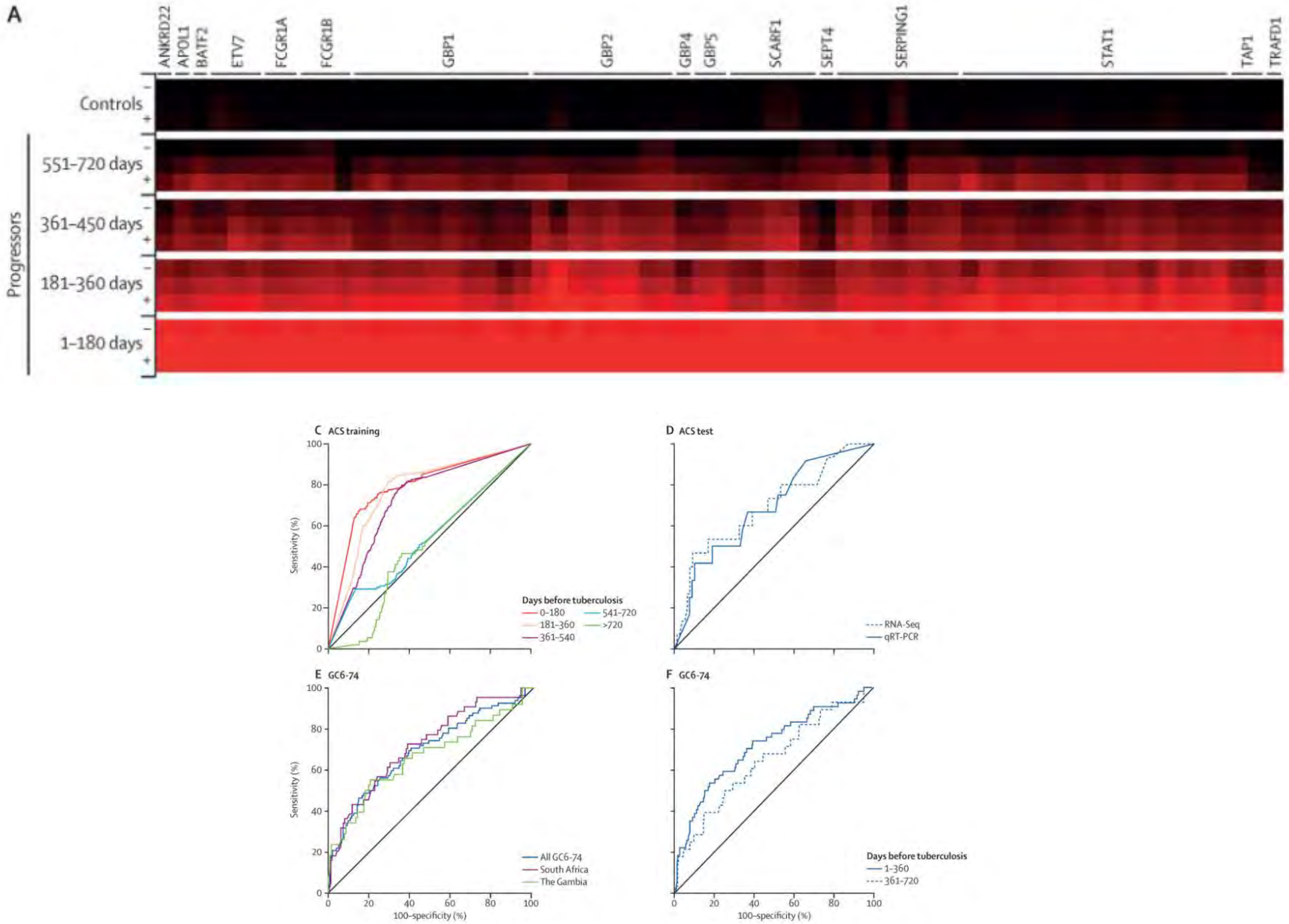


p=0.005 n=27


A
B
C
D
IGRA/TST
+
+
+
+
Latent tuberculosis
Active tuberculosis

THE LANCET
Volume 387, Issue 10035, 4–10 June 2016, Pages 2312-2322




A
ANKRD22
APOL1
BATF2
ETV7
FCGR1A
FCGR1B
GBP1
GBP2
GBP4
GBP5
SCARF1
SEPT4
SERPING1
STAT1
TAP1
TRAFD1
Controls
Progressors
551–720 days
361–450 days
181–360 days
1–180 days
C ACS training
Sensitivity (%)
Days before tuberculosis
0–180
181–360
361–540
541–720
>720
D ACS test
RNA-Seq
qRT-PCR
E GC6-74
All GC6-74
South Africa
The Gambia
100–specificity (%)
F GC6-74
Days before tuberculosis
1–360
361–720
100–specificity (%)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

The Correlate of Risk Targeted Intervention Study (CORTIS)

- Treatment Efficacy [Time Frame: 15 months]Treatment efficacy (TE) will be evaluated by comparing the incidence of endpoint-defined TB disease over 15 months in treated COR+ versus untreated COR+ participants.
- Performance of COR [Time Frame: 15 months]The performance of the COR will be evaluated by comparing the cumulative incidence of endpoint-defined TB disease over 15 months in untreated COR+ versus untreated COR- participants

Recruitment Information	
Recruitment Status ICMJE	Active, not recruiting
Actual Enrollment ICMJE (submitted: December 20, 2018)	2927
Original Estimated Enrollment ICMJE (submitted: April 6, 2016)	3200
Estimated Study Completion Date	December 31, 2019
Estimated Primary Completion Date	December 31, 2019 (Final data collection date for primary outcome measure)

- Treating LTBI currently is infeasible (need to treat >10 healthy people to prevent 1 cases)
- Diagnostics are within reach that will rapidly identify those at highest risk for disease development
- Even 2 months of treatment in otherwise healthy people is operationally difficult and unscalable
- “test and treat” would enable TB eradication strategies based on campaigns in hot-spots globally

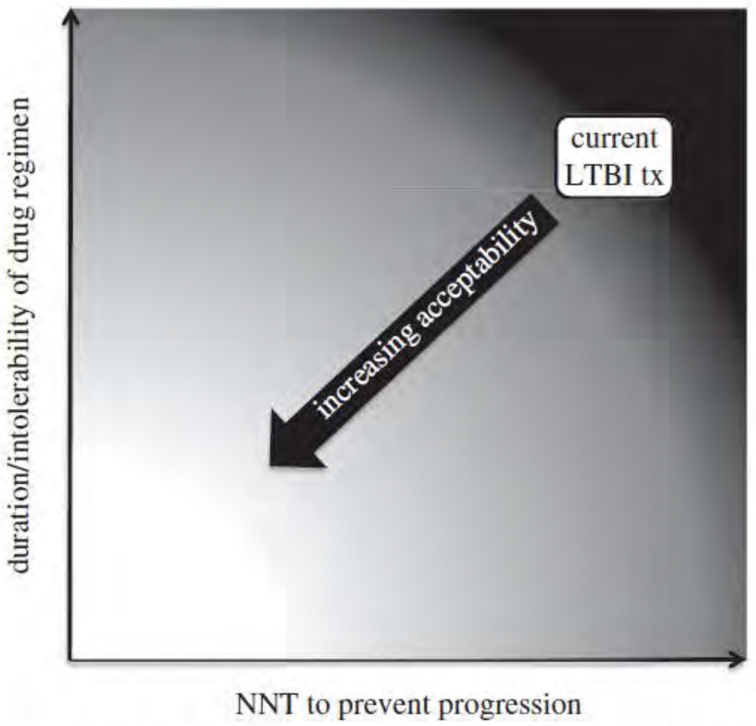


Figure 4. Acceptability of treatment relates to the duration and tolerability of treatment and the likelihood of benefit (prevention of progression to active disease). Improvements in drug regimens and/or improvements in predictability of diagnostic tests should lead to improved acceptability of treating LTBI.

CDC Latent TB Treatment Regimens

Drugs	Duration	Interval	Minimum-doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid and Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

*Use Directly Observed Therapy (DOT)

https://www.cdc.gov/tb/publications/factsheets/treatment/ltbitreatmentoptions.htm

CDC Active TB Treatment Regimens

	INTENSIVE PHASE		CONTINUATION PHASE				
Regimen	Drugs[a]	Interval and Dose[b] (minimum duration)	Drugs	Interval and Dose[b,c] (minimum duration)	Range of Total Doses	Comments[c, d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	Greater
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	Lesser
4	INH RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	

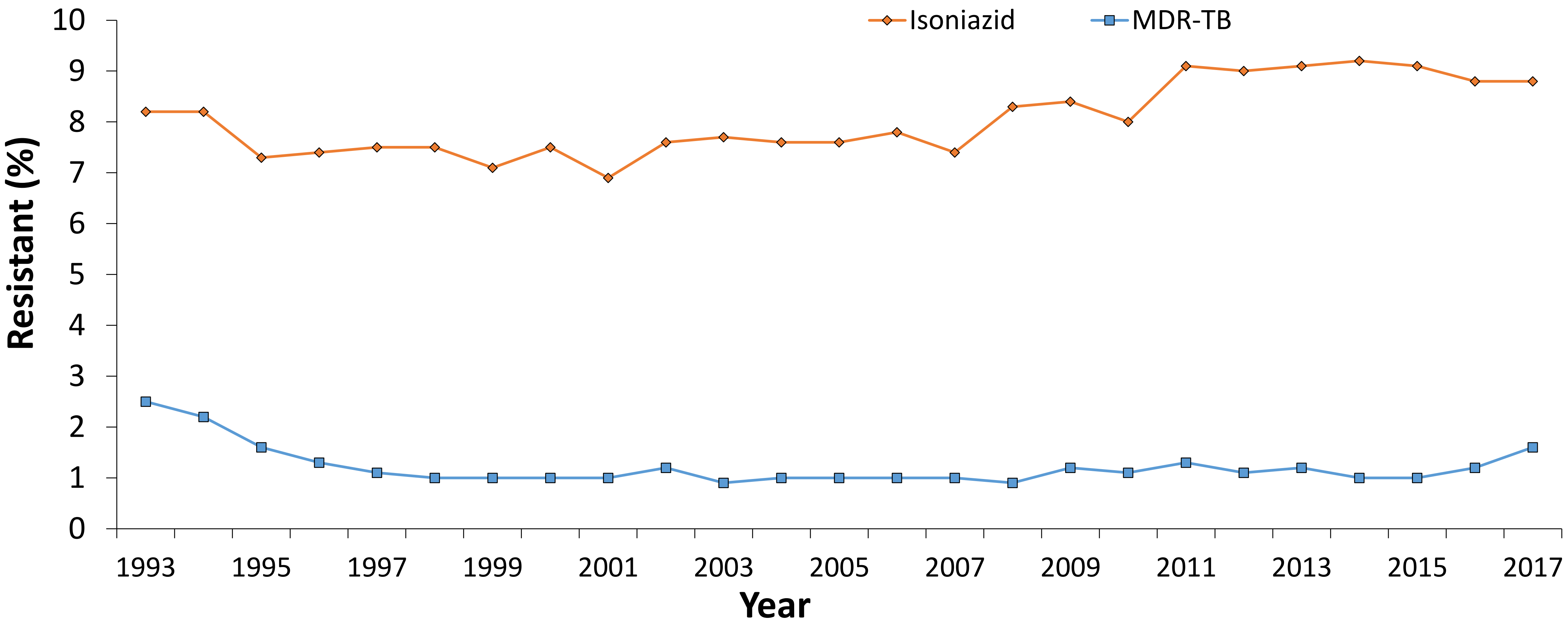
https://www.cdc.gov/tb/topic/treatment/tbdisease.htm

Drug Resistance

Resistance Pattern	Drugs Resistant To	Treatment Duration
Drug sensitive (DS)	None	6 months
Multi-drug resistant (MDR)	Isoniazid, Rifampin	9-12 months (no additional resistance) 18-20 months
Extensively-drug resistant (XDR)	Isoniazid, Rifampin, Fluoroquinolones, 2nd line injectable agents	20+ months

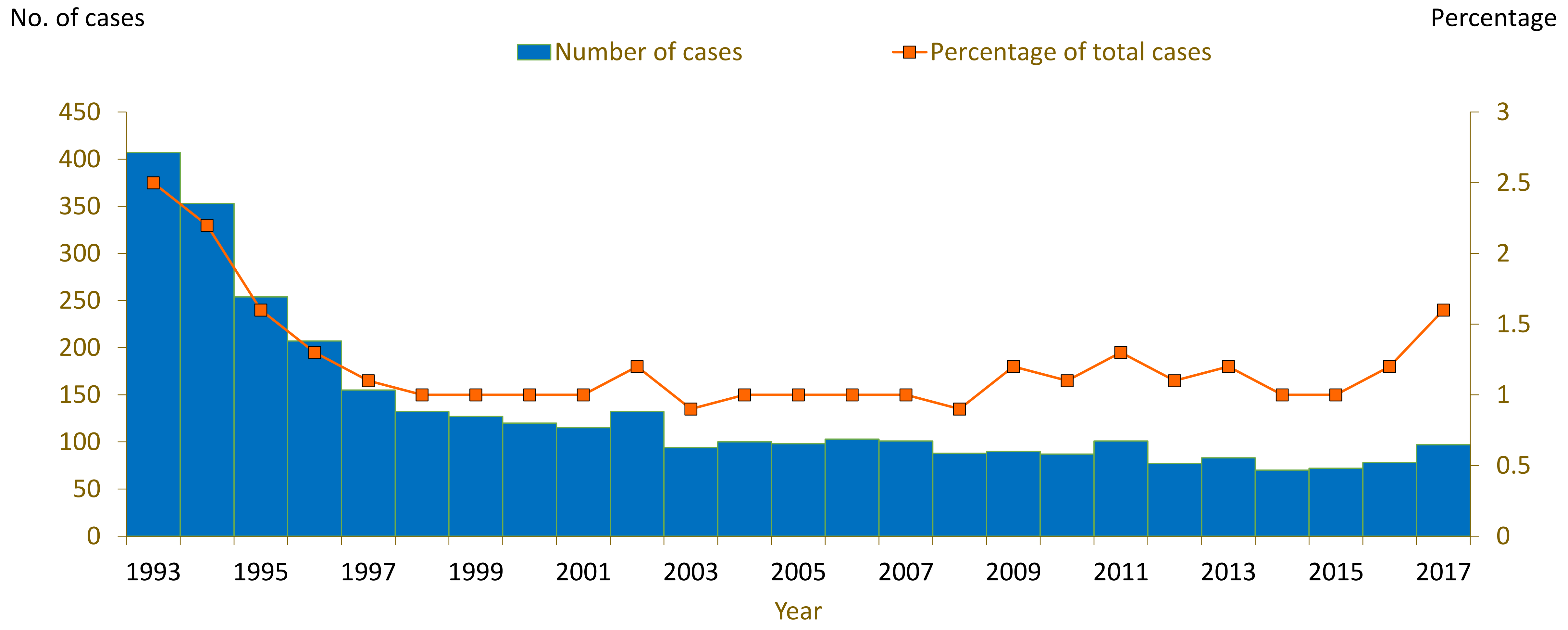
- Drug resistance can develop due to:
  - Poor drug adherence causing inadequate drug concentration levels which allows overgrowth of resistant bacterial mutants
  - Primary transmission of a drug resistant TB strain
- 2017: estimated 3.5% of new cases and 18% previously treated cases were MDR-TB

Primary Anti-TB Drug Resistance, United States, 1993–2017*



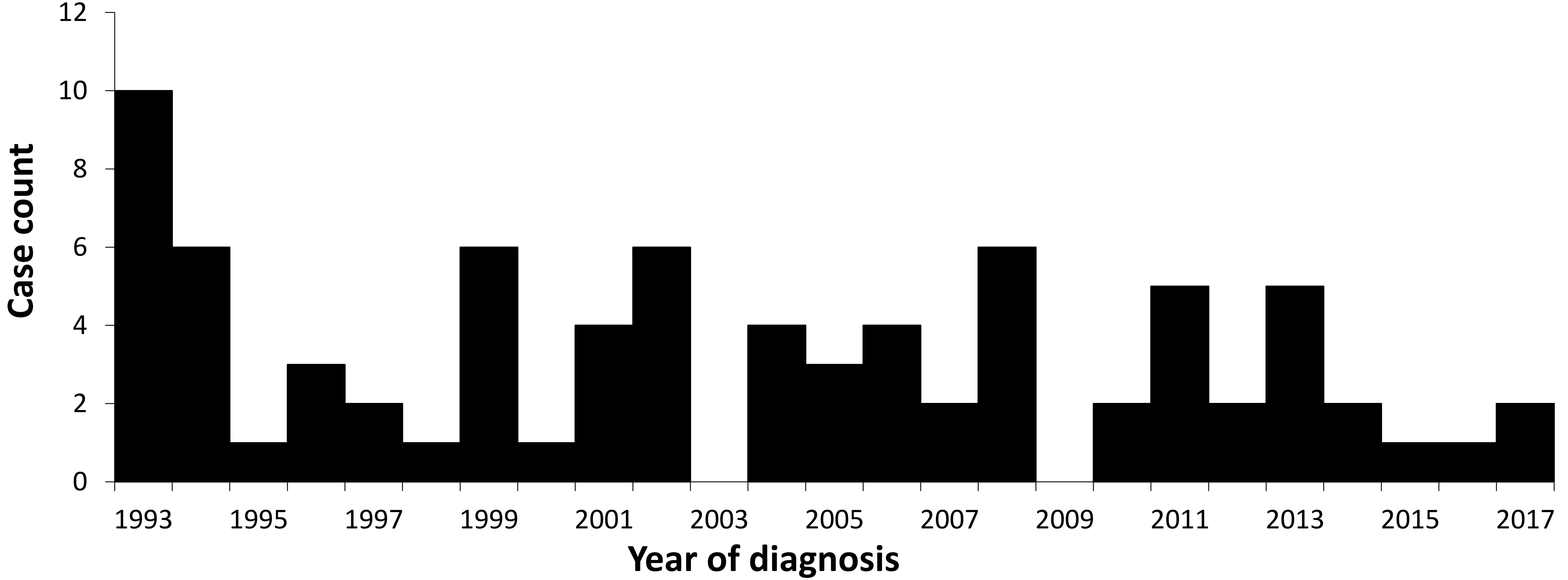
* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.

Primary MDR-TB, United States, 1993–2017*



* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.

XDR TB* Case Count, Defined on Initial DST,† by Year, 1993–2017§



* XDR TB, extensively drug-resistant TB.

† DST, drug susceptibility test.

§ XDR TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.

Global MDR-TB Rates

FIG. 3.20

Percentage of new TB cases with MDR/RR-TB[a]

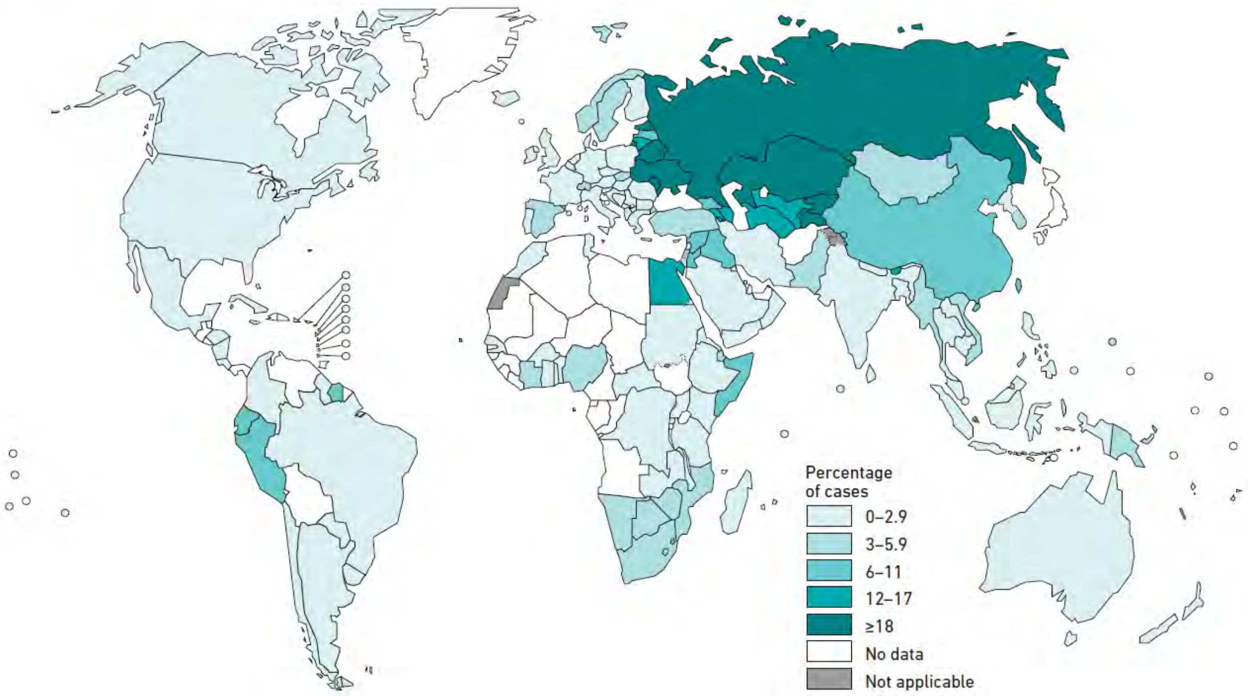
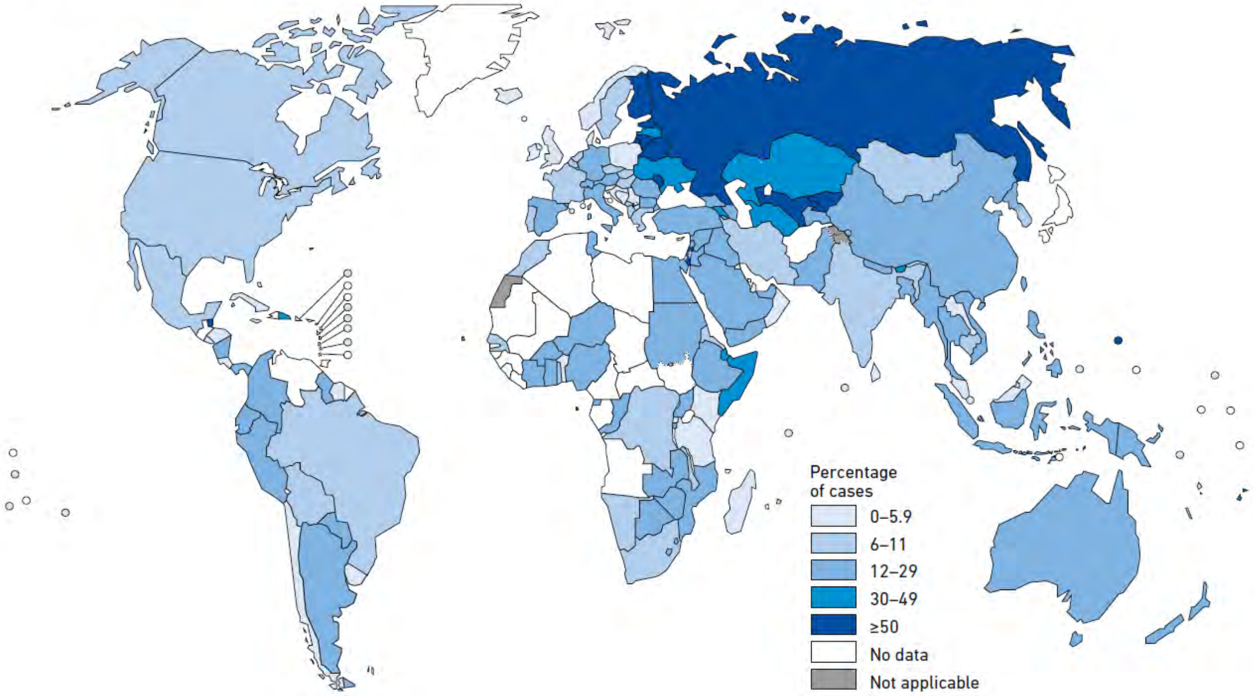


FIG. 3.21

Percentage of previously treated TB cases with MDR/RR-TB[a]



WHO. Global Tuberculosis Report 2018.

WHO MDR-TB Treatment Guidelines

- Treat for 18-20 months
- Include ≥5 drugs considered to be effective

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

WHO. Rapid communication: key changes to treatment of MDR- and RR-TB. August 2018.

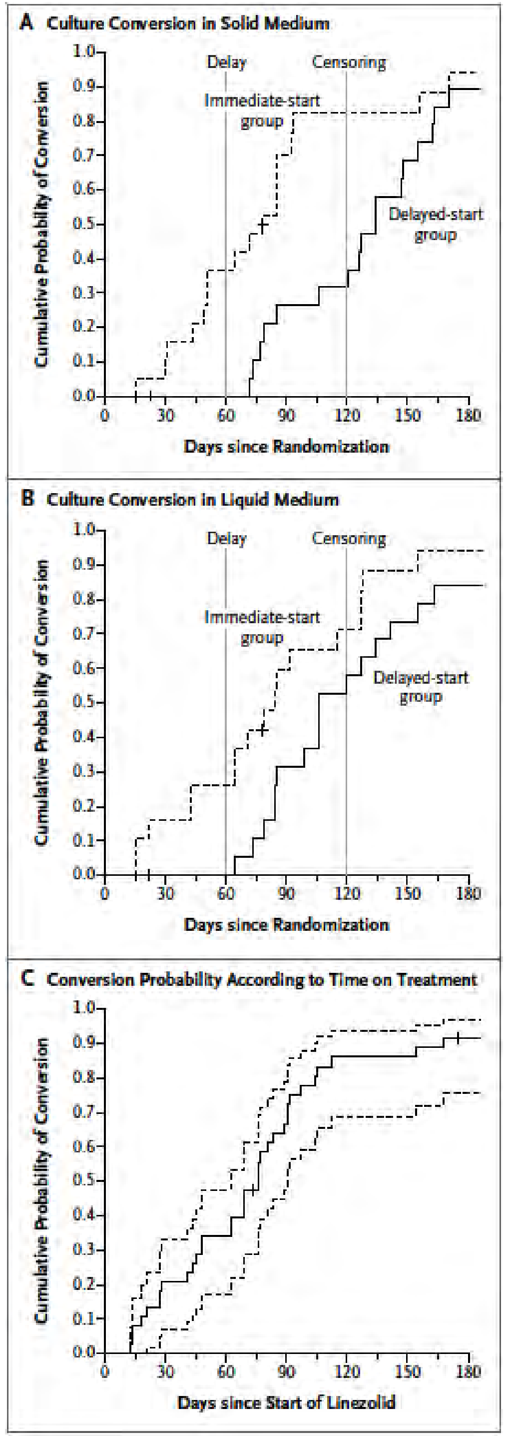
TABLE 5.1 **WHO recommended grouping of anti-TB drugs**

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 1. First-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin[a]	Rfb
	Rifapentine[a]	Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b]	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3. Fluoroquinolones (FQs)[d]	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin[c]	Gfx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone[e]	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycin[g]	Clr

WHO MDR-TB Treatment

- Treatment principles:
  - Intensive phase should contain at least four 2nd-line drugs likely to be effective and PZA
  - Generally should include ≥1 drug from each class
  - Intensive phase should last ≥8 mo or ≥4 mo past cx conversion
  - Total treatment duration ≥20 mo or ≥12 mo past cx conversion

WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014.



Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

N ENGL J MED 367;16 NEJM.ORG OCTOBER 18, 2012

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D., Hongjo Choi, M.D., Seonyeong Min, R.N., Taeksun Song, Ph.D., Laura E. Via, Ph.D., Lisa C. Goldfeder, C.C.R.P., Eunhwa Kang, M.Sc., Boyoung Jin, R.N., Hyeeun Park, R.N., Hyunkyung Kwak, B.S., Hyunchul Kim, Ph.D., Han-Seung Jeon, M.S., Ina Jeong, M.D., Joon Sung Joh, M.D., Ray Y. Chen, M.D., Kenneth N. Olivier, M.D., Pamela A. Shaw, Ph.D., Dean Follmann, Ph.D., Sun Dae Song, M.D., Ph.D., Jong-Koo Lee, M.D., Dukhyoung Lee, M.D., Cheon Tae Kim, M.D., Veronique Dartois, Ph.D., Seung-Kyu Park, M.D., Sang-Nae Cho, D.V.M., Ph.D., and Clifton E. Barry III, Ph.D.

- 41 chronic pulmonary XDR-TB pts no response to background regimen x6 mo randomized add LZD immediately or after 2 mo
- 4 mo: 15/19 (79%) immediate, 7/20 (35%) delayed cx converted (P=0.001)
- 34/39 (87%) converted by 6 mo

N ENGL J MED 371;8 NEJM.ORG AUGUST 21, 2014

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*

- 160 patients with smear+ MDR-TB randomized to preferred background regimen (96 wks) plus BDQ vs placebo during initial 24 wks
- Week 24 culture conversion: 79% vs 58%, P=0.008
- Wk 120 cure rates: 58% vs 32%, P=0.003

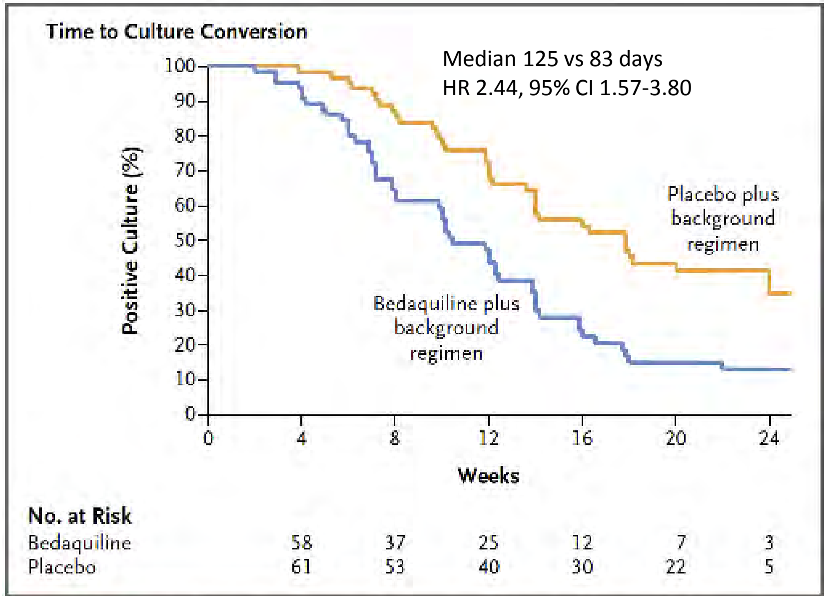


Figure 3. Time to Sputum-Culture Conversion in the Modified Intention-to-Treat Population.

Shown is the proportion of patients in each study group who had positive results on *Mycobacterium tuberculosis* culture during the 24-week investigational treatment phase of the study. Patients who withdrew from the study, who died, or who did not have sputum-culture conversion by week 24 were considered to have had treatment failure in the primary analysis, regardless of their culture status at the time of dropout or death. For these patients, data were censored at their last assessment, so the proportion of patients who had culture conversion cannot be derived from the data in the figure. Analysis based on a Cox proportional-hazards model with adjustment for study center and degree of radiographic lung cavitation showed significantly faster conversion in the bedaquiline group than in the placebo group at 24 weeks (P<0.001). The number of patients at risk at each time point is the number of patients who did not have culture conversion and who were still participating in the study.

TABLE 5.1 **WHO recommended grouping of anti-TB drugs (2014)**

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 1. First-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin[a]	Rfb
	Rifapentine[a]	Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b]	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3. Fluoroquinolones (FQs)[d]	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin[c]	Gfx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone[e]	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycin[g]	Clr

- Choose ≥5 active drugs including PZA
- Intensive phase ≥8 months
- Total treatment duration ≥20 months

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H[h]
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

2016:

- Groups reorganized
- Now allows for 9-12 mo regimen for MDR-TB with no additional resistance and no prior 2nd line treatment

GROUP	MEDICINE	Abbreviation
Group A: **Include all three medicines (unless they cannot be used)**	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: **Add both medicines (unless they cannot be used)**	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

2018:

Groups reorganized again now allowing for all oral regimen

FIG. 4.22

Treatment outcomes for new and relapse TB cases in 2016, 30 high TB burden countries, WHO regions and globally

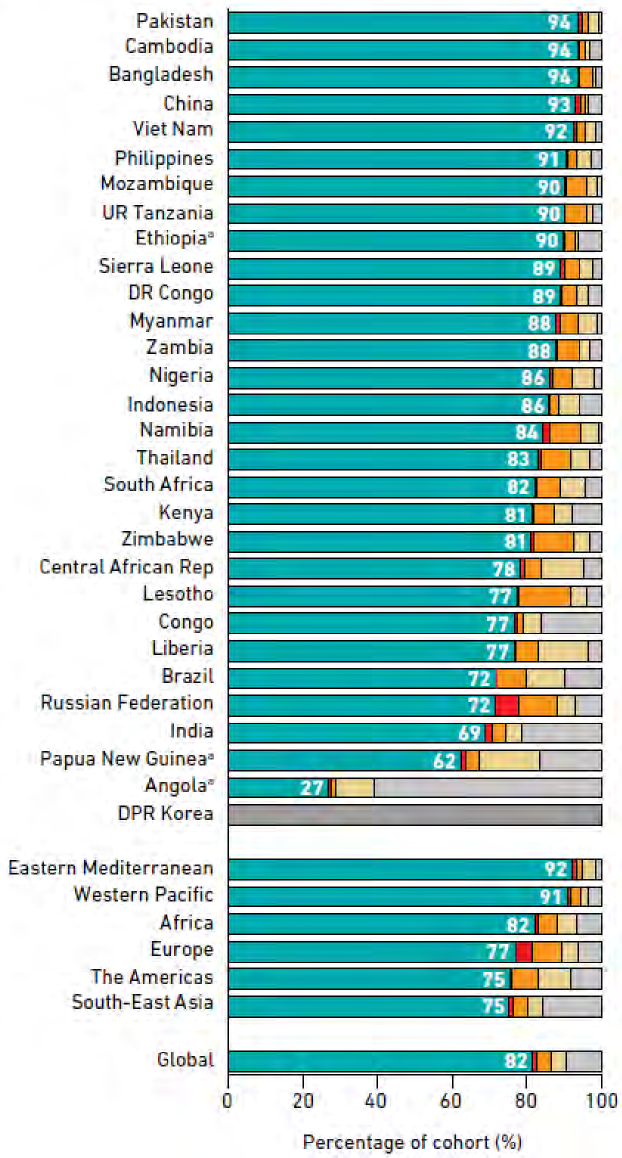
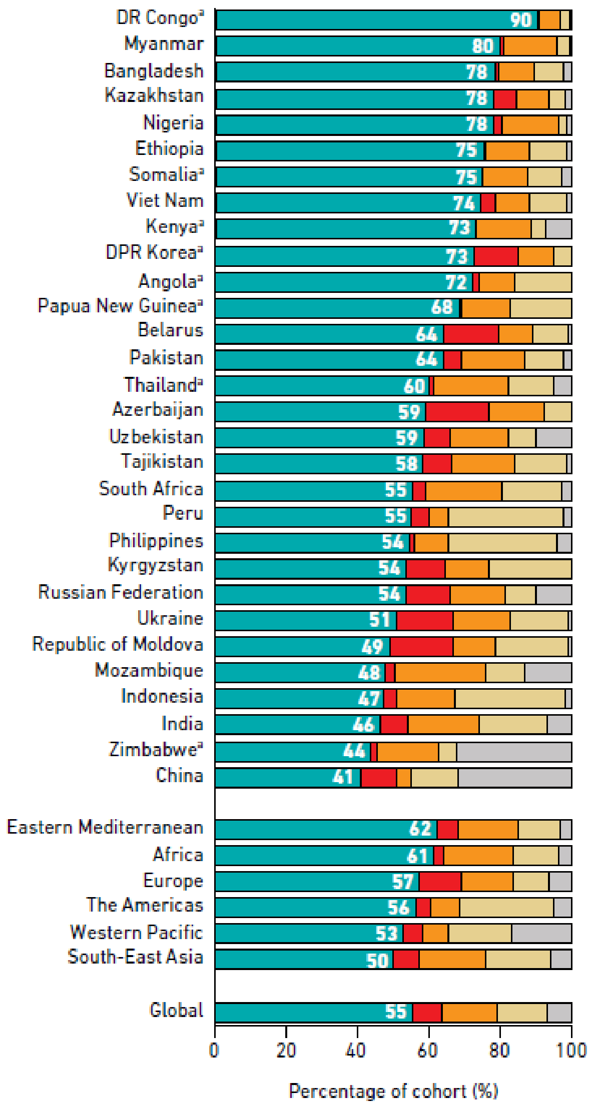


FIG. 4.26

Treatment outcomes for MDR/RR-TB cases started on treatment in 2015, 30 high MDR-TB burden countries, WHO regions and globally



Treatment success | Failure | Died | Lost to follow-up | Not evaluated | No data reported

Global TB Treatment Outcomes

XDR-TB treatment outcomes:

- 34% treatment success
- 19% treatment failure
- 26% died
- 21% lost to follow-up or not evaluated

WHO. Global Tuberculosis Report 2018.

Global Treatment Coverage Rates

FIG. 4.16

Estimated TB treatment coverage (new and relapse patients as a percentage of estimated TB incidence) in 2017, 30 high TB burden countries, WHO regions and globally

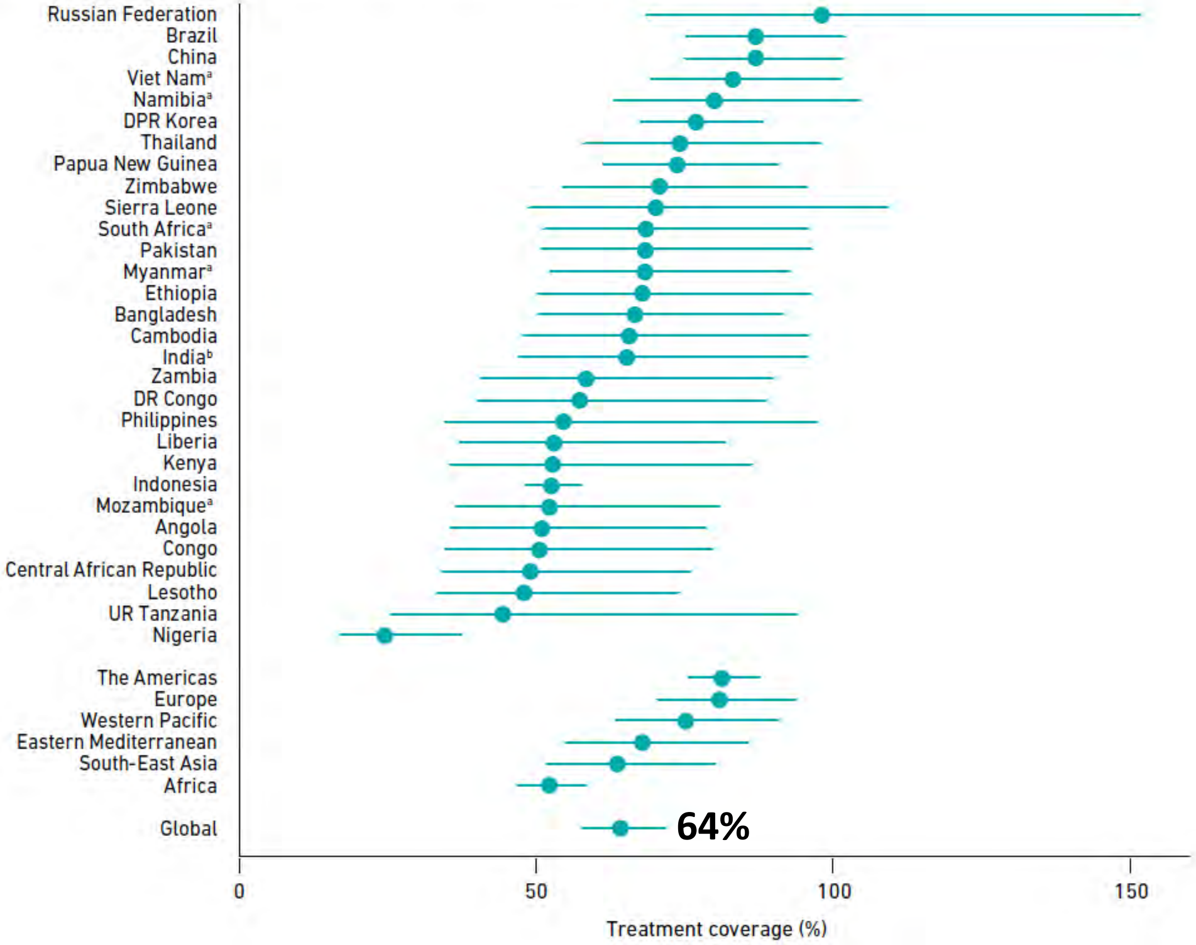
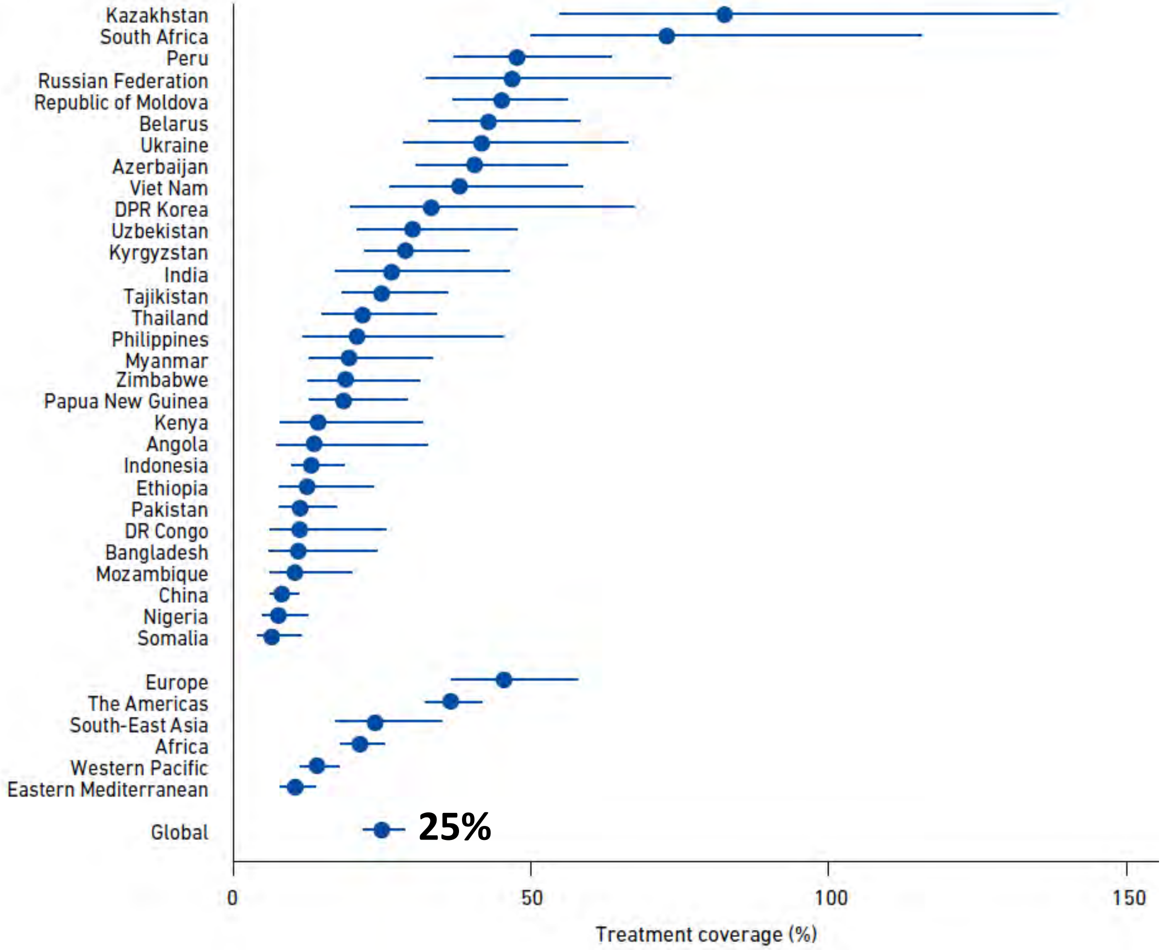


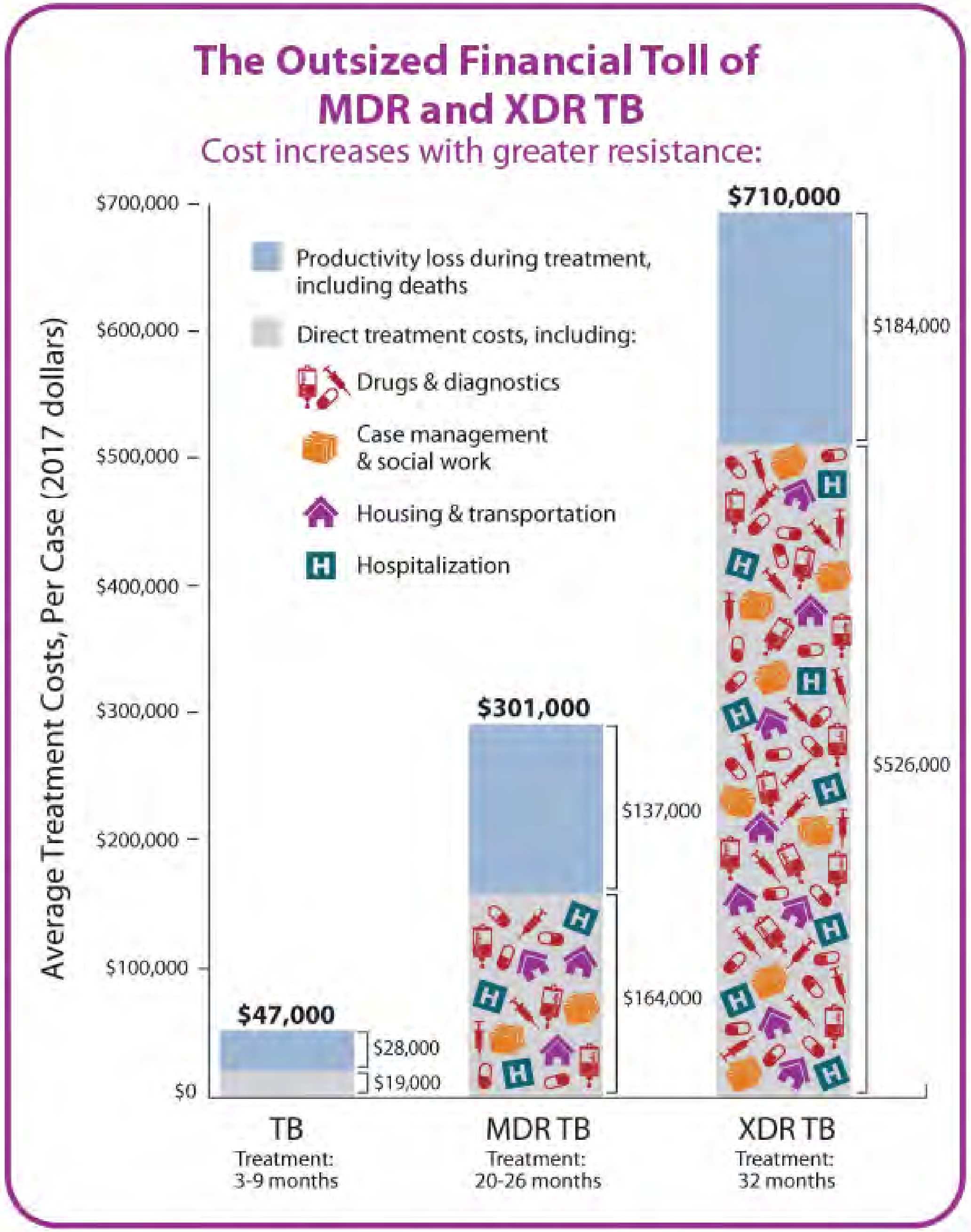
FIG. 4.20

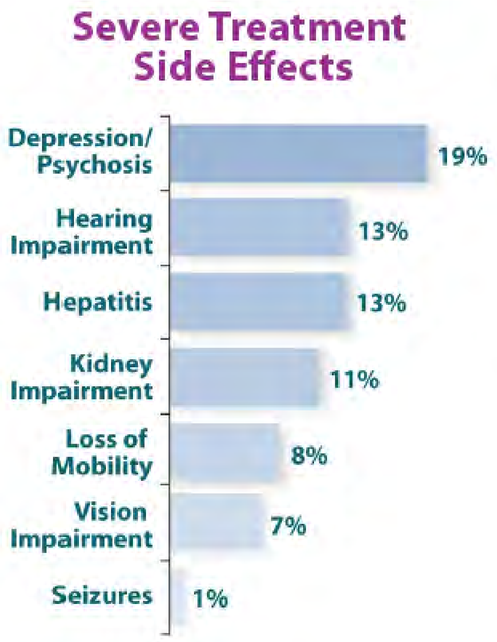
Estimated treatment coverage for MDR/RR-TB (patients started on treatment for MDR-TB as a percentage of the estimated incidence of MDR/RR-TB) in 2017, 30 high MDR-TB burden countries, WHO regions and globally



WHO. Global Tuberculosis Report 2018.

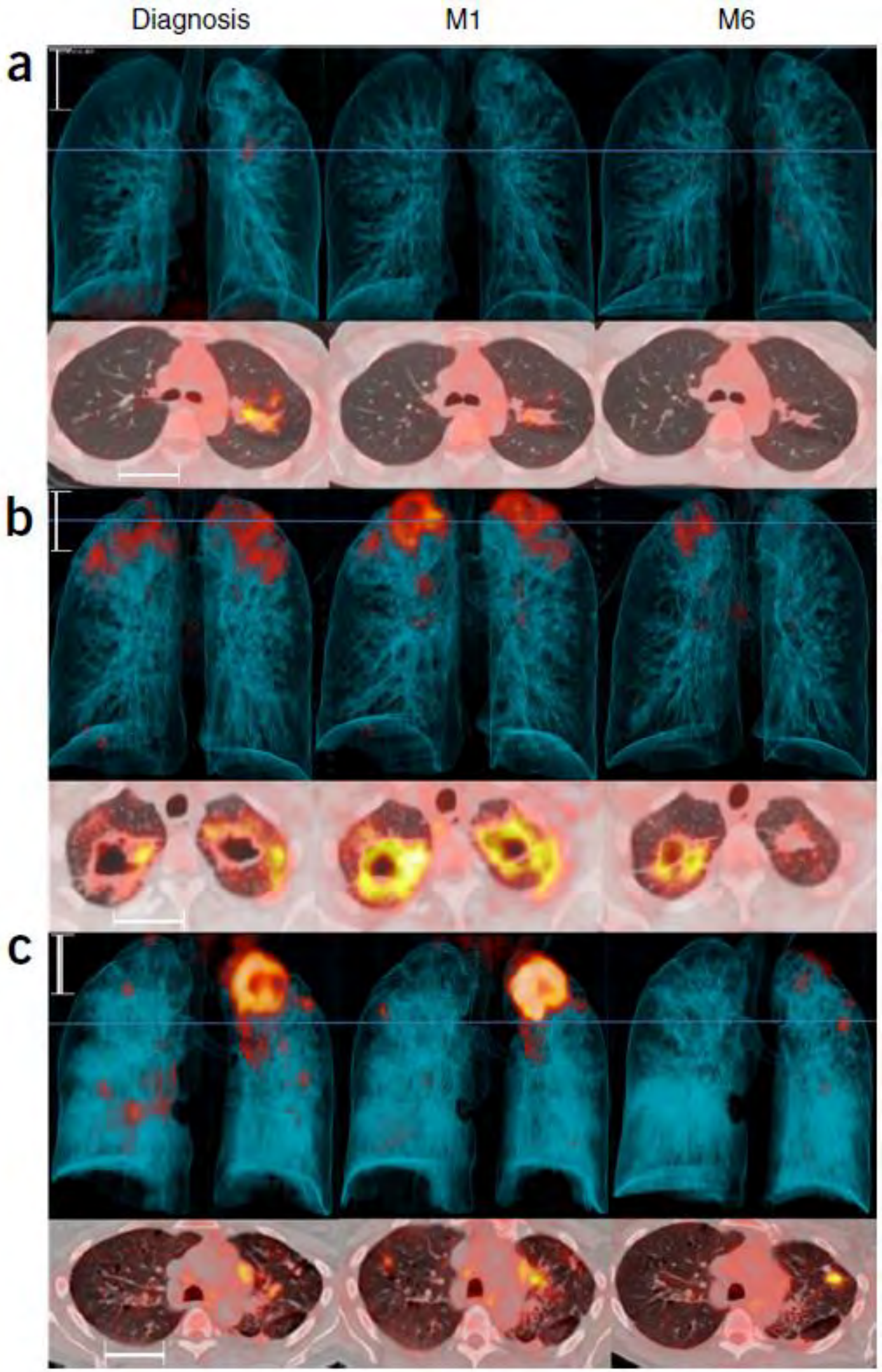
Cost of TB Treatment





https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/costly-burden-dr-tb-508.pdf

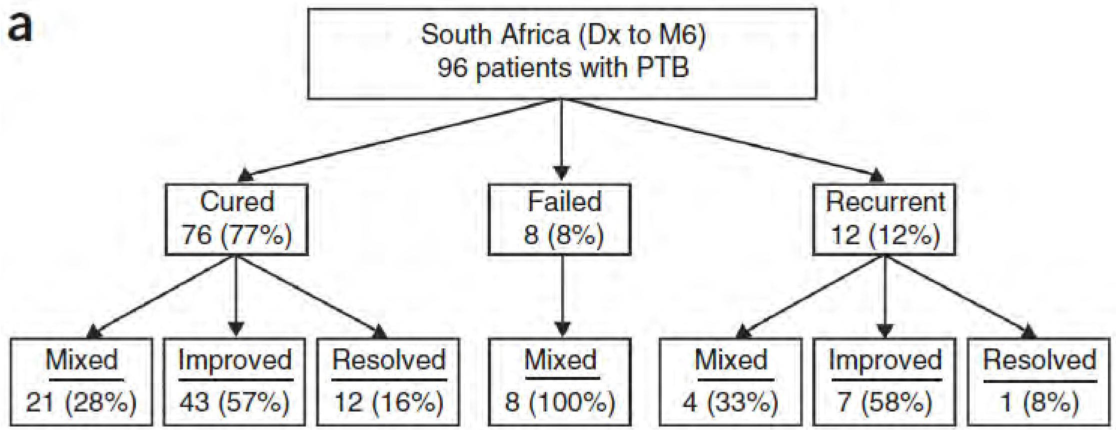
Host Factor Affecting Cure



Cure: resolved
14/99 (14%)

Cure: improved
(persistent uptake)
51/99 (52%)

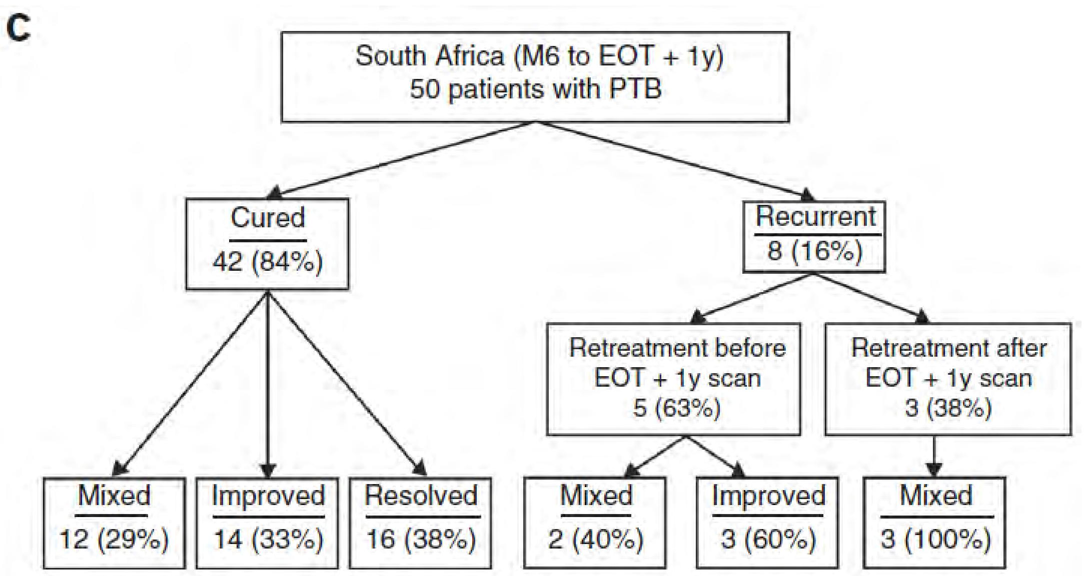
Cure: mixed
response
(new/increased
intensity)
34/99 (34%)



3 patients missing treatment outcome

Malherbe ST. Nat Med 2016;22(10):1094-1100.

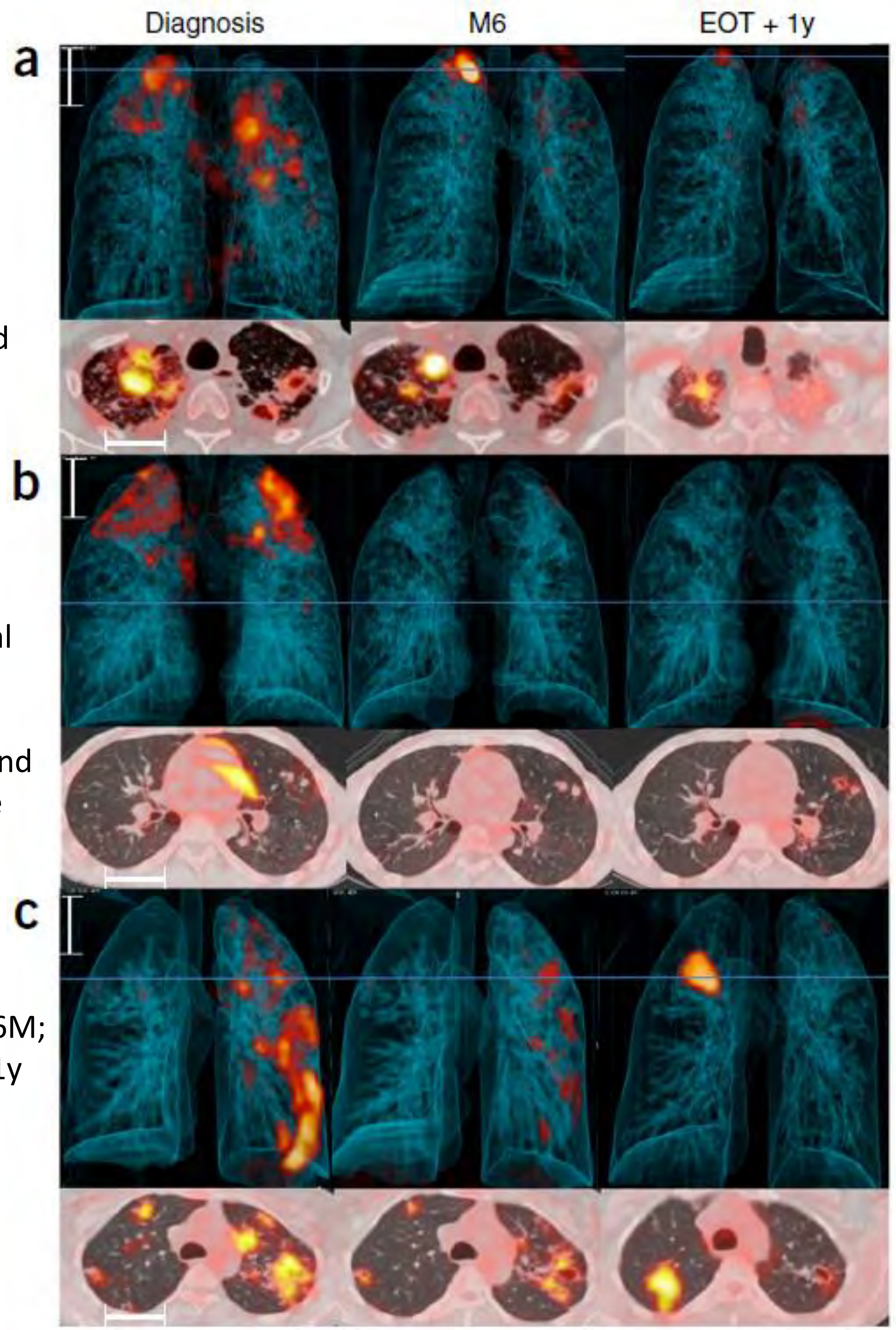
Host Factor Affecting Cure



Cure: new M6 lesion, improved 1y later

Cure: M6 residual nodules, no PET uptake; 1y later with cavitation and increased uptake

Residual uptake at 6M; new consolidation 1y later but cx-; cx+ 6 mo later

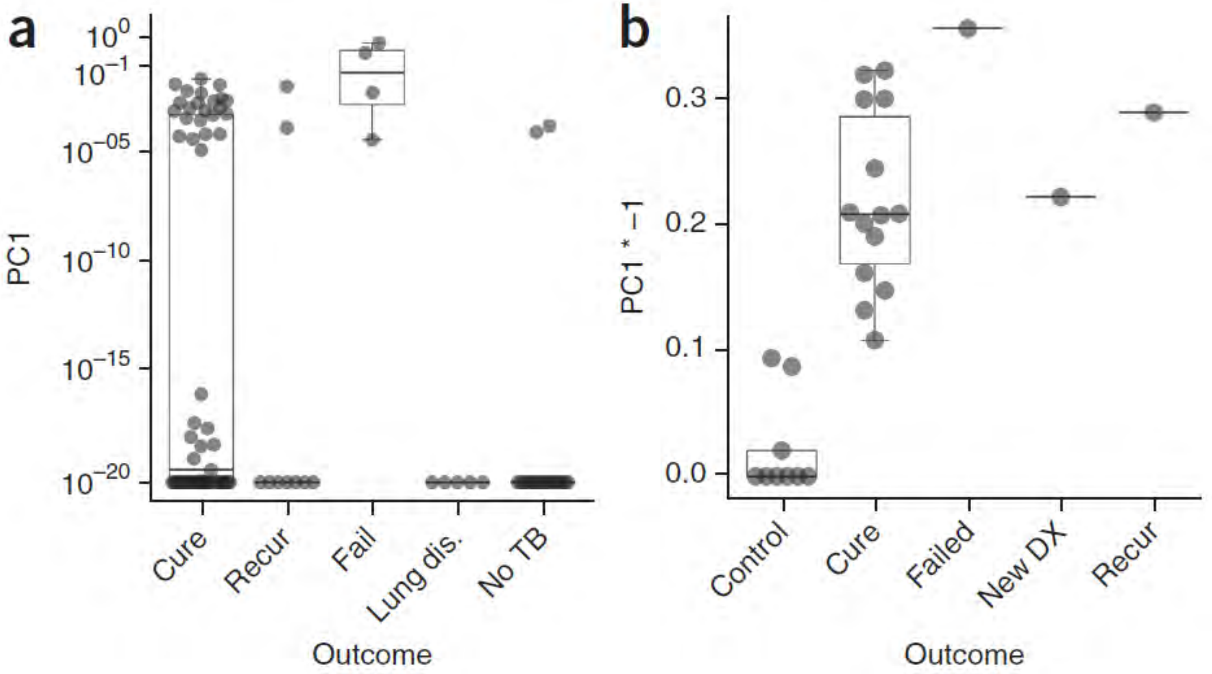


Malherbe ST. Nat Med 2016;22(10):1094-1100.

Host Factor Affecting Cure

M6 sputum with detectable Mtb mRNA:
- 22/60 (37%) cured
- 4/4 failed
- 2/9 (22%) recurrent TB
- 0/5 other lung diseases
- 2/20 (10%) healthy controls

Figure 5

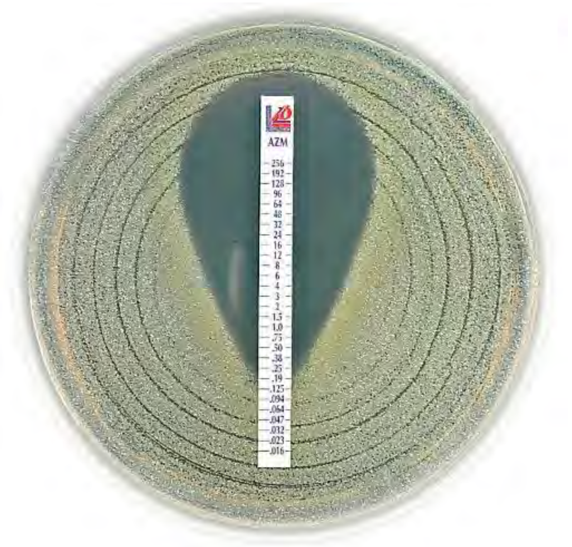


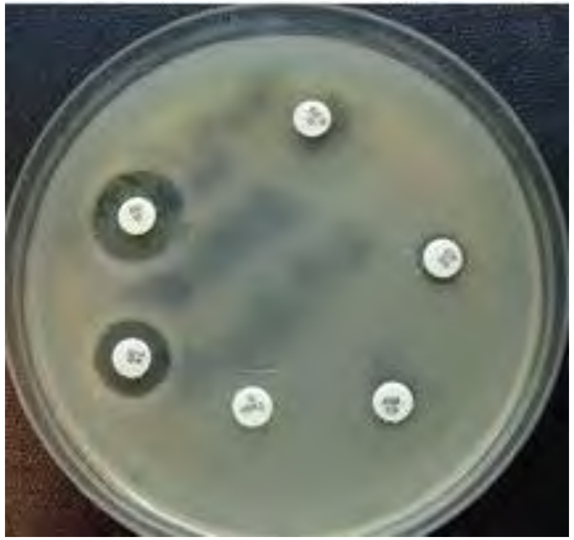
EOT BAL with detectable Mtb mRNA:
- 14/14 cured
- 1/1 failed
- 1/1 newly diagnosed TB
- 1/1 recurrent TB
- 2/10 controls (1 subsequently dxed with TB)

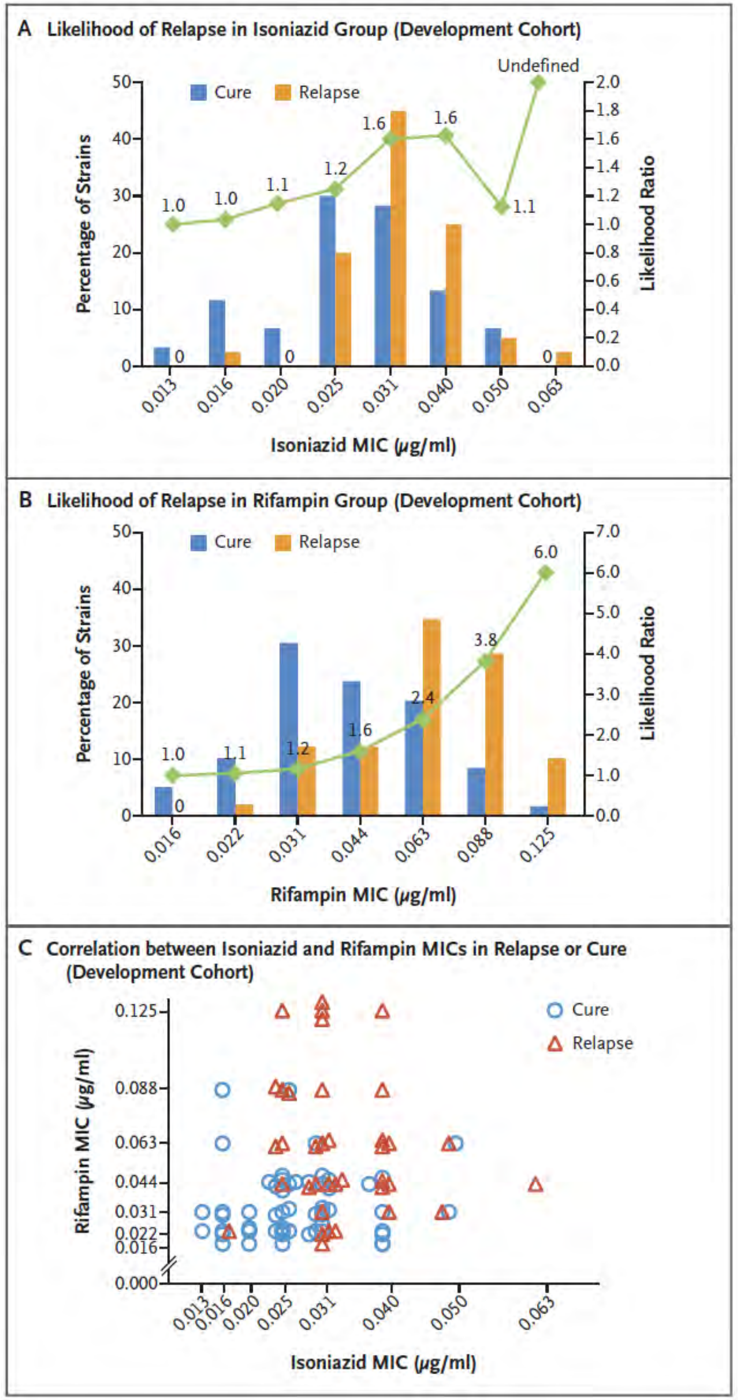
Malherbe ST. Nat Med 2016;22(10):1094-1100.

Bacterial Factor Affecting Cure: MIC

- Minimum inhibitory concentration (MIC): the lowest concentration of an antibiotic that prevents >99% growth in solid or liquid medium
- Resistance breakpoint: a chosen concentration of antibiotic which defines whether a bacteria is susceptible or resistant
  - MIC < breakpoint = susceptible
  - MIC = breakpoint = intermediate
  - MIC > breakpoint = resistant
  - INH = 0.1 μg/ml; RIF = 1.0 μg/ml







INH	mean MIC (±SD) µg/ml	Ratio (95% CI)	P
Relapse	0.0334 ±0.0085	1.17 (1.03-1.33)	0.02
Cure	0.0286 ±0.0092		

LR >1 Test result associated with disease
LR =1 Test result not helpful
LR <1 Test result associated with absence of disease

RIF	mean MIC (±SD) µg/ml	Ratio (95% CI)	P
Relapse	0.0695 ±0.0276	1.53 (1.27-1.86)	<0.001
Cure	0.0453 ±0.0223		

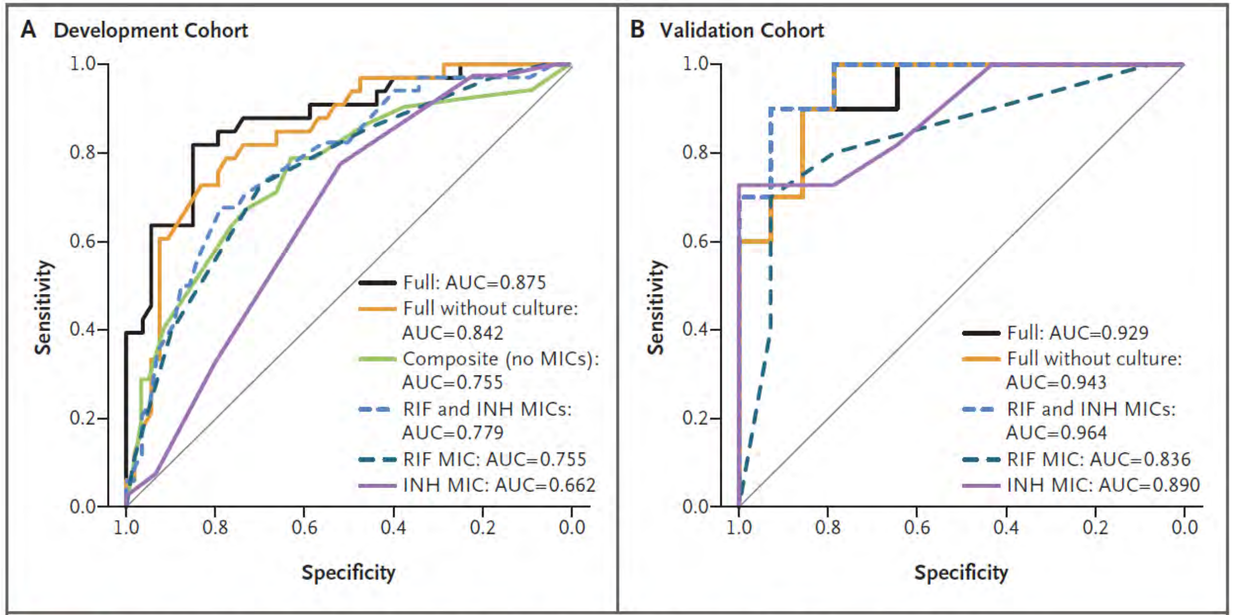


Figure 2. Receiver-Operating-Characteristic (ROC) Curves for Relapse after Tuberculosis Treatment.
Shown are ROC curves in the development cohort (Panel A) and the validation cohort (Panel B). Curves are displayed for MIC values of isoniazid (INH) and rifampin (RIF) alone, for MIC values of isoniazid plus rifampin, and for the other models discussed below, as indicated. ROC curves are graphical plots that illustrate the performance of a binary classifier system as its discrimination threshold is varied. The curves were created by plotting the true positive rate against the false positive rate at various threshold settings. The area under the curve (AUC) that is shown in each plot summarizes the overall biomarker performance in a single number, with 0.5 indicating no difference from chance and 1.0 indicating a perfect biomarker with sensitivity and specificity both equal to 100%. The full model includes the following factors: MIC values of isoniazid and rifampin, cavitary disease on radiography, being underweight, and a positive 8-week sputum culture. The full model without culture results includes the same covariates as the full model with the exclusion of a positive 8-week sputum culture. The composite model includes the same covariates as the full model with the exclusion of the MIC values of isoniazid and rifampin.

- Bacterial factors (INH/RIF sub-breakpoint MICs) predicted relapse just as well as all other significant host factors (cavity on CXR, underweight, wk 8 sputum cx+)
- A subpopulation of “drug-sensitive” *Mtb* may require a higher concentration of antibiotics for better treatment outcomes
- Combining host and bacterial factors are highly predictive of relapse and may be used to predict patients cured before 6 months of treatment
- Additional prospective studies are needed in larger cohorts

Colangeli R. NEJM 2018;379:823-833

TB Treatment Shortening

- British Medical Research Council (BMRC) conducted multiple trials in 1970s and 1980s to reduce treatment duration from 18 to 9 to 6 months, maintaining relapse rates 1-2%
- Attempts to shorten treatment below 6 months resulted in increased relapse rates so 6 months became established as the standard of care

Table V. Level of success of regimens of different duration in smear- and culture-positive disease

Duration of chemotherapy (months)	*Patients assessed**	*Bacteriological relapses*	*95% confidence limits*
9	298	3 (1%)	0.2–2.9
6	422	4 (1%)	0.3–2.4
$4\frac{1}{2}$–5	465	16 (3%)	2–6
4	364	43 (12%)	9–16
3	307	41 (13%)	10–18

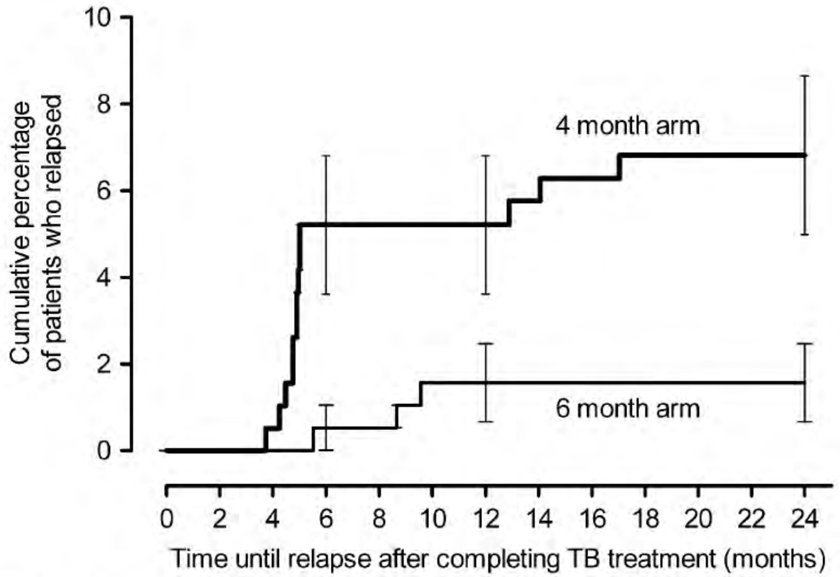
* The regimens and duration of follow-up are given in Tables II, III and IV. (The six-month and shorter durations all contain streptomycin, isoniazid, rifampicin and pyrazinamide.)

However, in view of the evidence that a very substantial majority, at least 80%, of patients with drug-sensitive infections are cured by three months of intensive four-drug chemotherapy, it is clear that even six-month regimens based on isoniazid, rifampicin and pyrazinamide are already unnecessarily long for most patients and a nine-month regimen even more so.

Fox W. Br J Dis Chest 1981; 75:331.

TB Treatment Shortening

- DMID 01-009 trial only shortened treatment to 4 mo among those with less severe disease:
  - No cavity on baseline CXR
  - Sputum culture converted to negative by 2 months of treatment
- Trial stopped early due to higher relapse rate in 4-mo arm compared to 6-mo arm (7.0% vs 1.6%, p<0.01)
- Despite study failure, 4-mo arm treatment success rate increased from about 80-85% to 93%



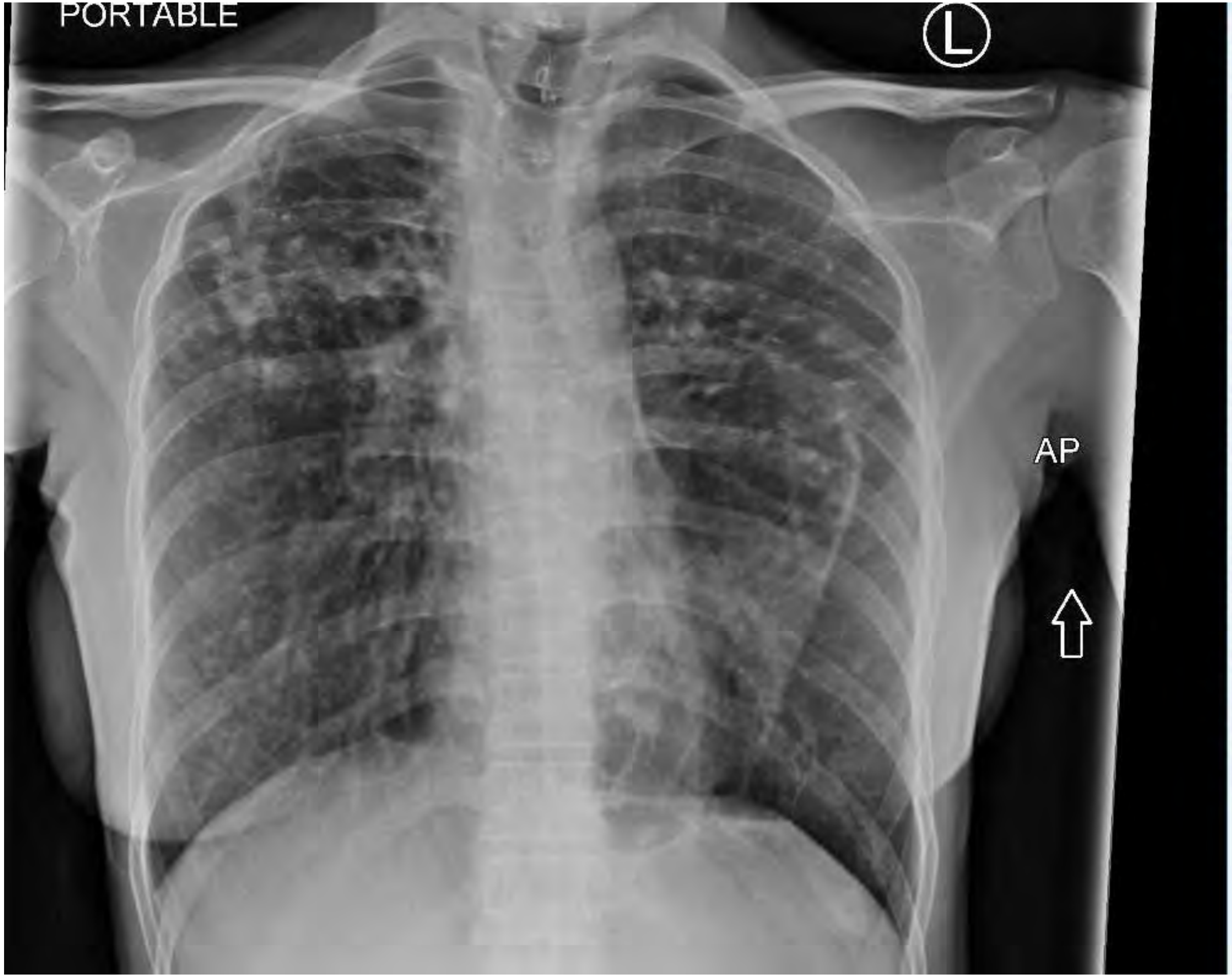
Number at Risk

6 Month Arm	193	193	191	190	187	184	182
4 Month Arm	193	193	192	181	178	174	173

Figure 2. Kaplan Meier curve showing the cumulative percentage of patients who relapsed after completing anti-tuberculosis (TB) treatment. The chi-square test for a difference in the percentage of patients who relapsed by treatment arm was significant ($P < 0.01$). *Error bars* represent the standard error of the mean percentage of patients who relapsed at 6, 12, and 24 months of follow-up after completing treatment.

Johnson JL. Am J Respir Crit Care Med 2009;180(6):558-63.

Sensitivity of CXR for Cavities



CLINICAL INDICATION: Active pulmonary tuberculosis infection causing shortness of breath. Clinical Evaluation. pulmonary TB ;

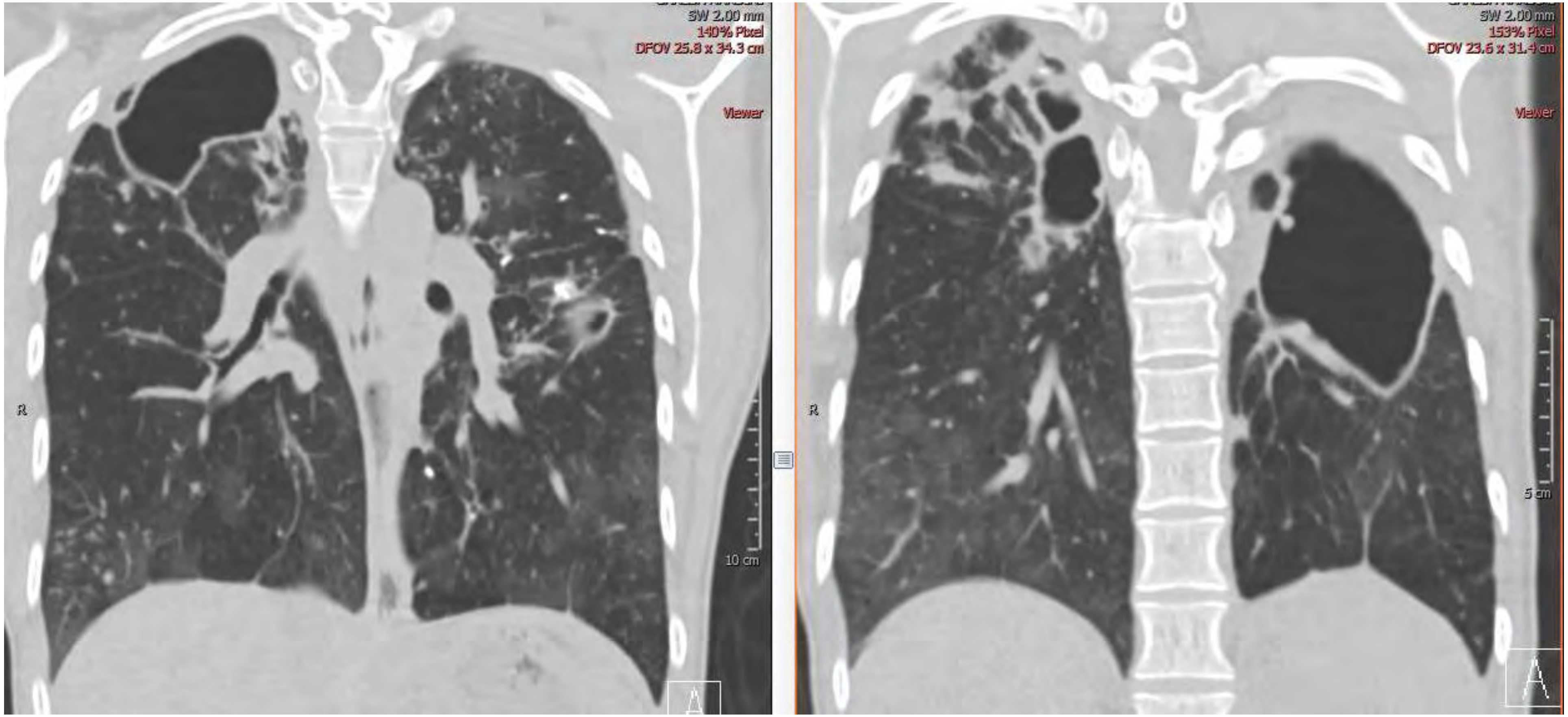
TECHNIQUE: Chest AP one view

COMPARISON: No prior chest radiograph available for comparison

FINDINGS::
Nodular opacities in the upper lungs consistent with history of tuberculosis.
Linear scarring ill-defined opacity in both mid and lower lungs, with architectural distortion in the right perihilar region, also due to tuberculosis infection.
Nodularity in the left mid and lower lung.
Cardiac silhouette within normal radiographic limits.
Probable mediastinal paratracheal mediastinal soft tissue thickening.
Skeletal structures intact without focal destructive osseous disease.

IMPRESSION:
Nodular densities in the upper lungs and left perihilar region with extensive linear scarring and architectural distortion in the perihilar regions, consistent with history of tuberculosis.

CT Scan


SW 2.00 mm
140% Pixel
DFOV 25.8 x 34.3 cm
Viewer
R
10 cm
SW 2.00 mm
153% Pixel
DFOV 23.6 x 31.4 cm
Viewer
R
5 cm

Predict TB

DMID 01-009

- Baseline: no cavity on CXR
- Treatment response:
  - Month 2 sputum culture negative

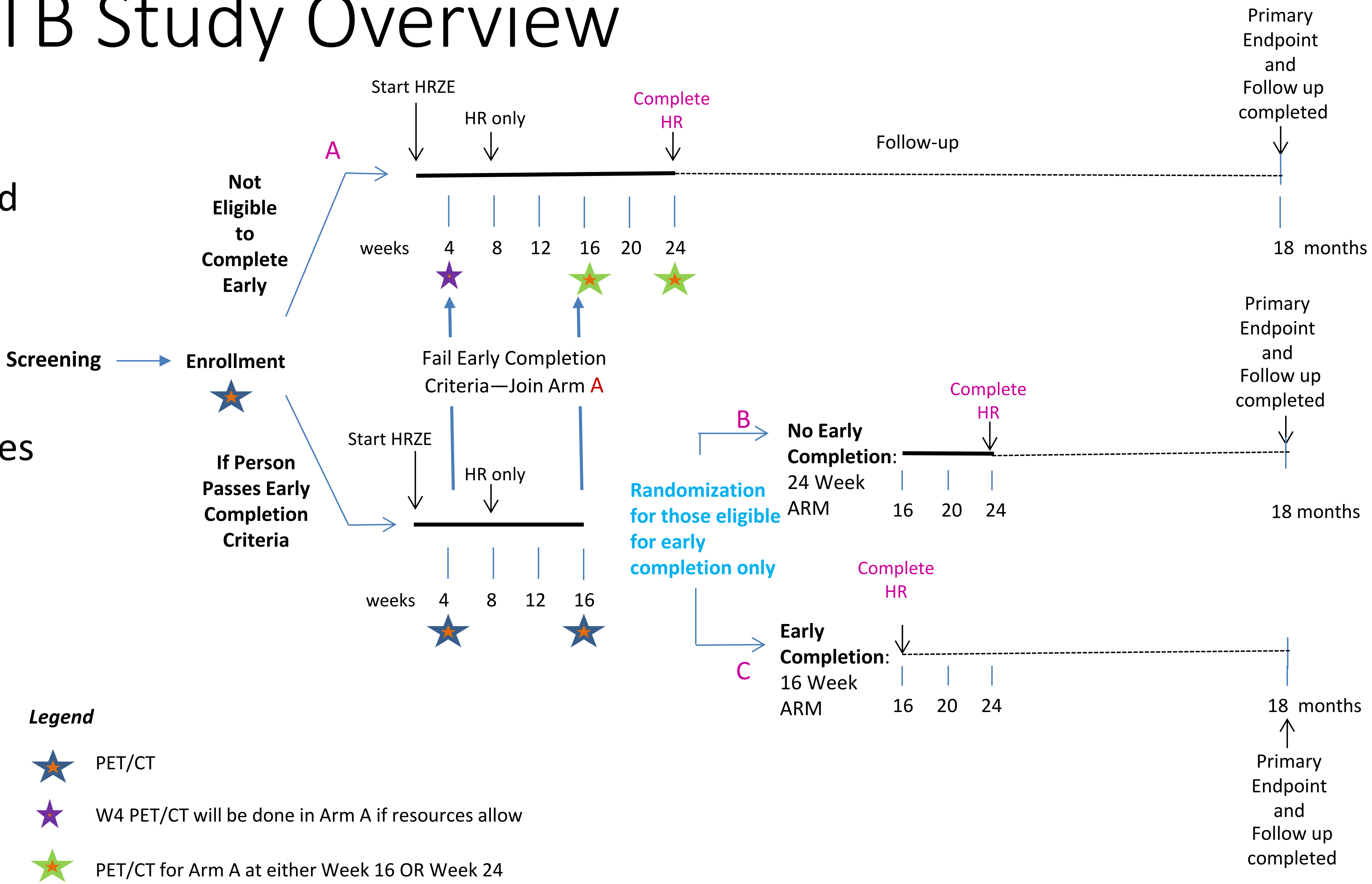
Predict TB

- Baseline: PET/CT burden of disease
- Treatment response:
  - Month 1 PET/CT burden of disease
  - Month 4 Xpert MTB/RIF cycle threshold

Study	4-month Treatment Success Rate
Prior studies (no stratification)	80-85%
DMID 01-009	93%
Predict TB	?

Predict TB Study Overview

- Partially randomized phase 2 study;
- Sample size: 310 in Arms B and C combined
- Inclusion criteria: adults; HIV-; diabetes negative
- Locations:
    - Cape Town, South Africa;
    - Henan, China



Predict TB Acknowledgements

China
- Henan BOH 河南省卫计委
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- Xinmi CDC 新密市结核病防治所
    - JIN Xiaowei 靳晓伟
- Xinxiang CDC 新乡市结核病防治所
    - ZHANG Ruanqing 张软青
- Fudan University 复旦大学
    - GAO Qian 高谦
- Sino-US Henan Project Office 中美结核研究办公室
    - ZHU Hong 朱红
    - GAO Jingcai 高静彩
    - LI Baobao 李宝宝
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    - Madeleine Hanekom
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    - Kim Narunsky
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    - Sandra Mukasa
- UCT SATVI
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    - Terry Nugent

- Rutgers New Jersey Medical School
    - David Alland

- Colorado State University
    - John Belisle

- Catalysis Foundation for Health
    - Jill Winter

PREDICT-TB FUNDING PARTNERS

PredictTB

BILL & MELINDA GATES foundation

EDCTP

NIH National Institutes of Health
Turning Discovery Into Health

National Natural Science Foundation of China

Grand Challenges China

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Science and Technology of the People's Republic of China

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FNIH
Foundation for the National Institutes of Health

LINQ.
management GmbH

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The TB Drug Accelerator (TBDA)

The TBDA is a groundbreaking partnership between eight pharmaceutical companies, seven research institutions, and a product development partnership that seeks to develop a new TB drug regimen through collaboration in early-stage drug discovery research.

CORRESPONDENCE

Linezolid for XDR-TB — Final Study Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

July 16, 2015
N Engl J Med 2015; 373:290-291
DOI: 10.1056/NEJMc1500286

An exemplar TBDA project: TB oxazolidinone optimization

- Improve Mtb potency by >10x → lower dose
- Limited cross-antibacterial activity
- ↑ MPS & MAO selectivity → improve safety index
- High caseum free fraction & good penetration (low clogP)
  - Profile compounds with various degree of physiochemical properties
- Predicted human PK similar or better than that of linezolid

MERCK & CO., INC.
Kenilworth, N.J., U.S.A.

David Olsen
Katherine Young
Charles Garlisi
Lihu Yang
Richard Tschirret-Guth
Christopher Boyce
Jacqueline Fine
Julian Ehrhart

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BILL & MELINDA GATES foundation

NIH National Institute of Allergy and Infectious Diseases

Helena Boshoff
Kriti Arora
Patricia Tsang
Vee Tan
Andaleeb Sajid
Yumi Park
Garreth Prosser
Sangmi Oh

LO ROP: Oxazolidinones (TBDA)

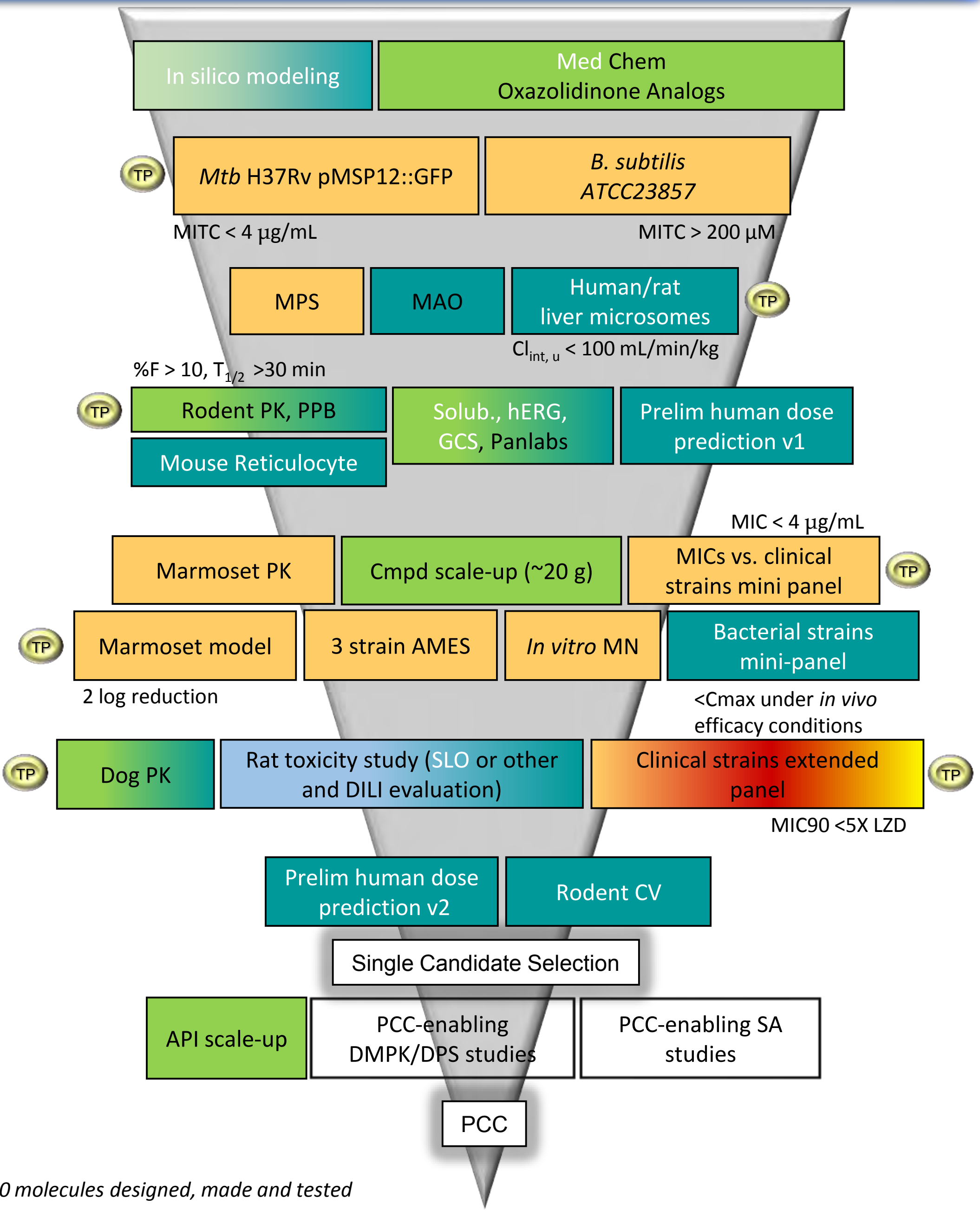
ROP Refresh: October 2015v2

SCREENING (Hit Package Delivery)

uHTS	ALIS	FRAG	PHENO
NIAID 1/14, 12/14 MRL 6/15	7/30/15	N/A	N/A

Ad Hoc Assays	
TBDA cross-screening	CS
Cross-resistance with LZD-R strains	CS
Kill curves with Mtb	CS
FOR/Resistance selection (Mtb; ≤Rif FOR)	CS
Analog mutants: Target specific sequencing	CS
Analog mutants: Whole genome sequencing	CS
Caseum penetration	CS
ELF measurements	LC
Mtb/Macrophage activity	CS
Epithelial lung fluid MIC reversal	LC
Compound tissue distribution	LC
Mouse model	LC
MML	CS
Click-iT Edu cytotoxicity	CS
HepG2 cytotoxicity	CS

CS: Compound specific (<10%)
MO: Monthly (>10%)
LC: Lead candidates only

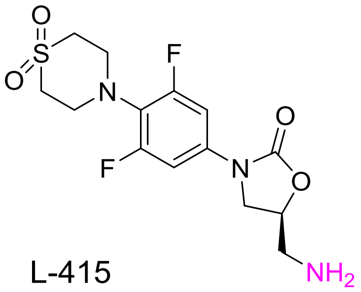


Ca 1000 molecules designed, made and tested

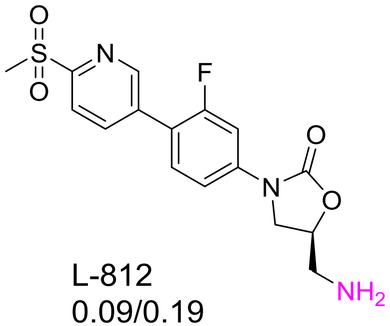
TIER: 1, 2, 3, 4a, 4b, 5, 6, 7

	Max Cmpd Flow/Stage	Time (WK)
1	25	1
2	15	3
3	10	2
4	6	2
5	3	4
6	2	3
7	1	16
Total Wk		31

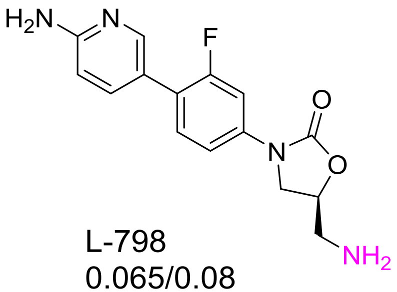
High FOR was associated with C-5 amines and mutation in Rv0133



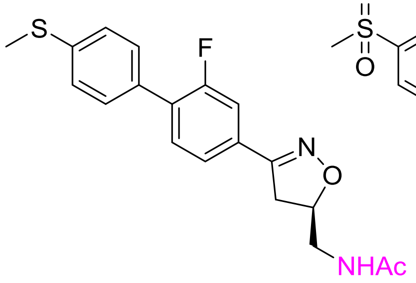
L-415
0.14/0.39 (Mtb)
>200 (B.s.)



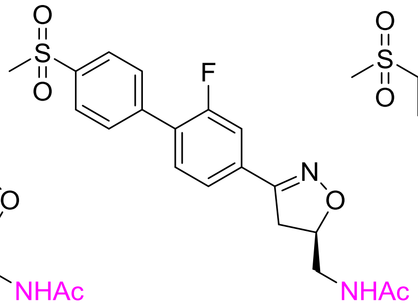
L-812
0.09/0.19
>200



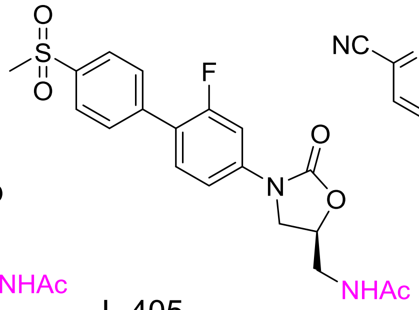
L-798
0.065/0.08
200



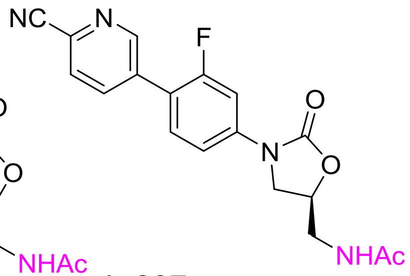
L-421
0.19/0.04
200



L-857
0.78/0.78
0.39



L-405
0.09/0.14
0.20



L-287
0.14/0.14
0.20

FOR is ~ 10^{-6}

Same MOA?

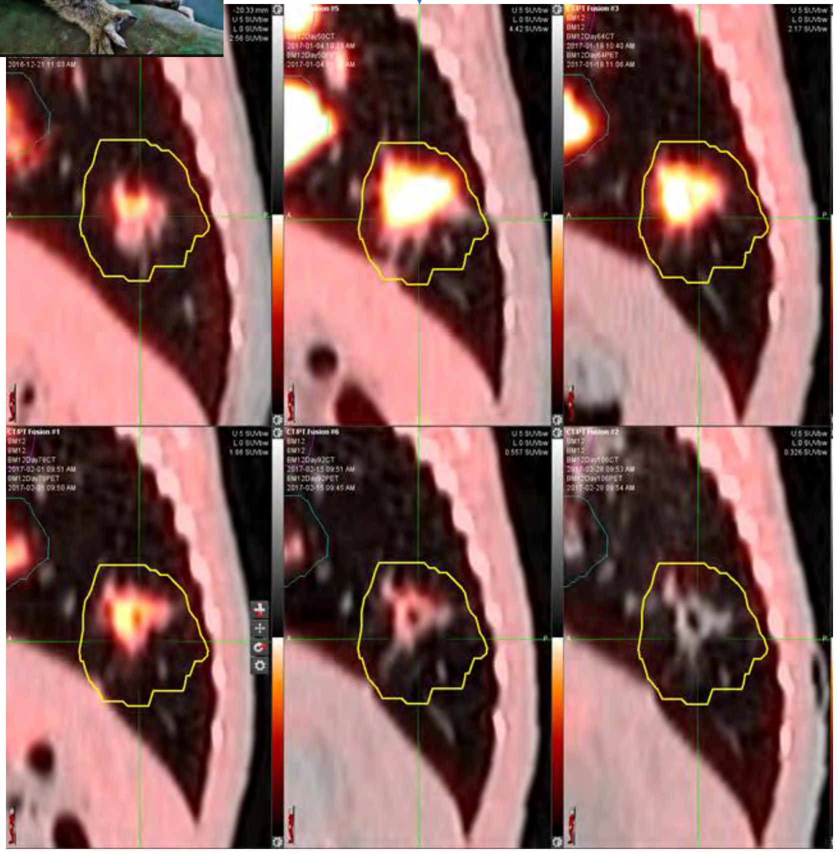
FOR is ~ 10^{-9}

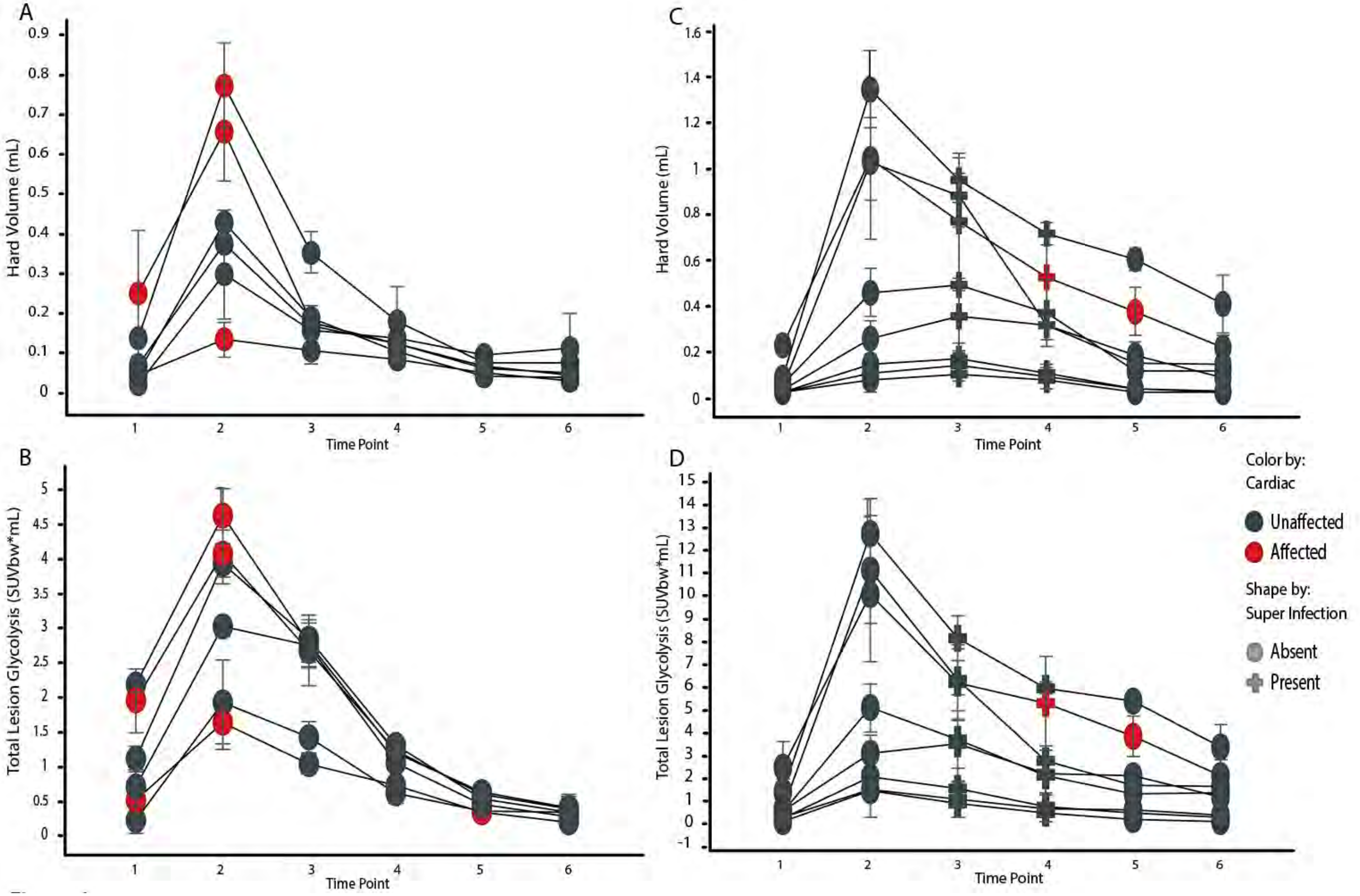
	Acetamide	Amine
Acetamide-R	R	R
Amine-R	S	R

- **9/14 TB “Oxa-amine” resistant mutants mapped to Rv0133**

662 rapidly sterilizes lesions in marmosets

Rx Start

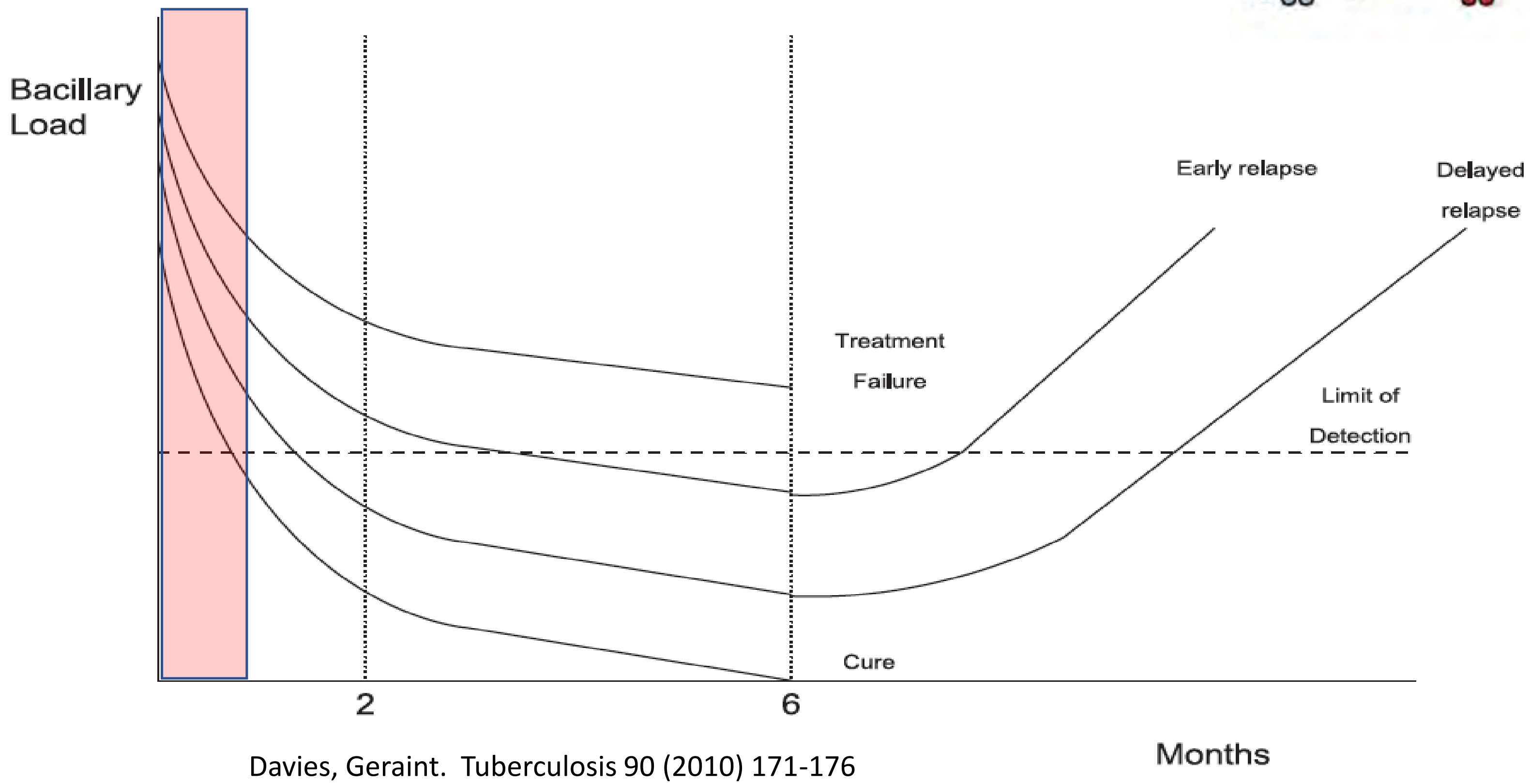




How to reliably triage which drugs/regimens proceed to resource- intense Phase III trials?

Early Bactericidal Activity (EBA)

Daily decline in sputum CFU associated with an investigative drug or regimen given for up to **14 days**



Davies, Geraint. Tuberculosis 90 (2010) 171-176

NexGen EBA Trial in Cape Town, South Africa

Enrollment of 160 drug-naïve, HIV-negative adults with smear-positive tuberculosis from Cape Town, South Africa.

8 treatment arms;
20 patients per arm

1. INH
2. RIF
3. PZA
4. MXF
5. RIF + PZA
6. INH + PZA
7. INH + RIF + PZA + EMB
8. MXF + RIF + PZA +EMB

“INH” – isoniazid; “RIF”-rifampin; “PZA”-pyrazinamide, ”EMB”-ethambutol, “MXF”-moxifloxacin

Screen/Enroll **Discharge**

1-2 Baseline | **14 days of study treatment (8 arms) Inpatient monitoring**

Baseline Overnight Sputum | **Daily overnight sputum collection (CFU count and Time to Positivity)**

Baseline PET/CT | **14 day PET/CT**

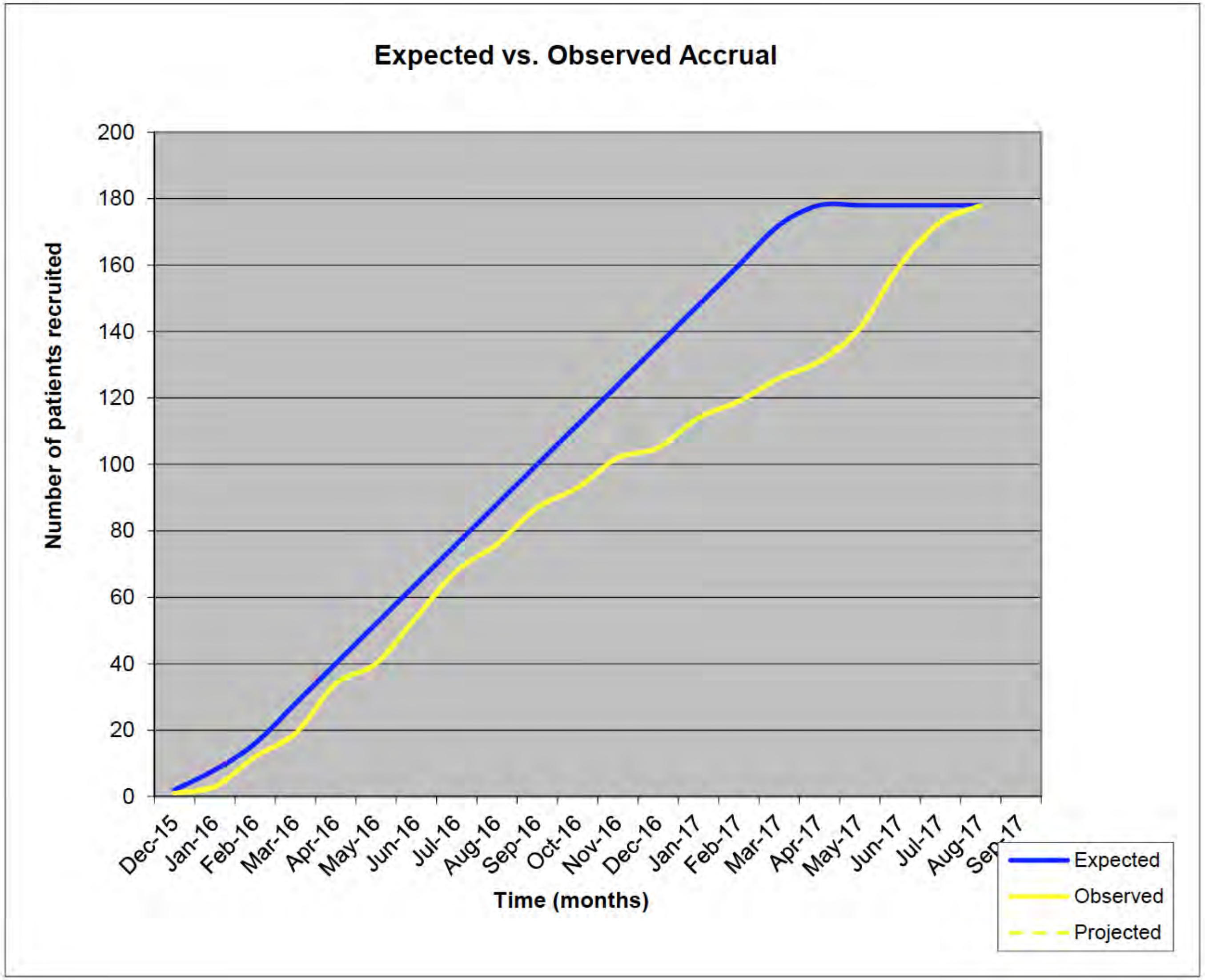
Baseline blood | **14-day Blood**

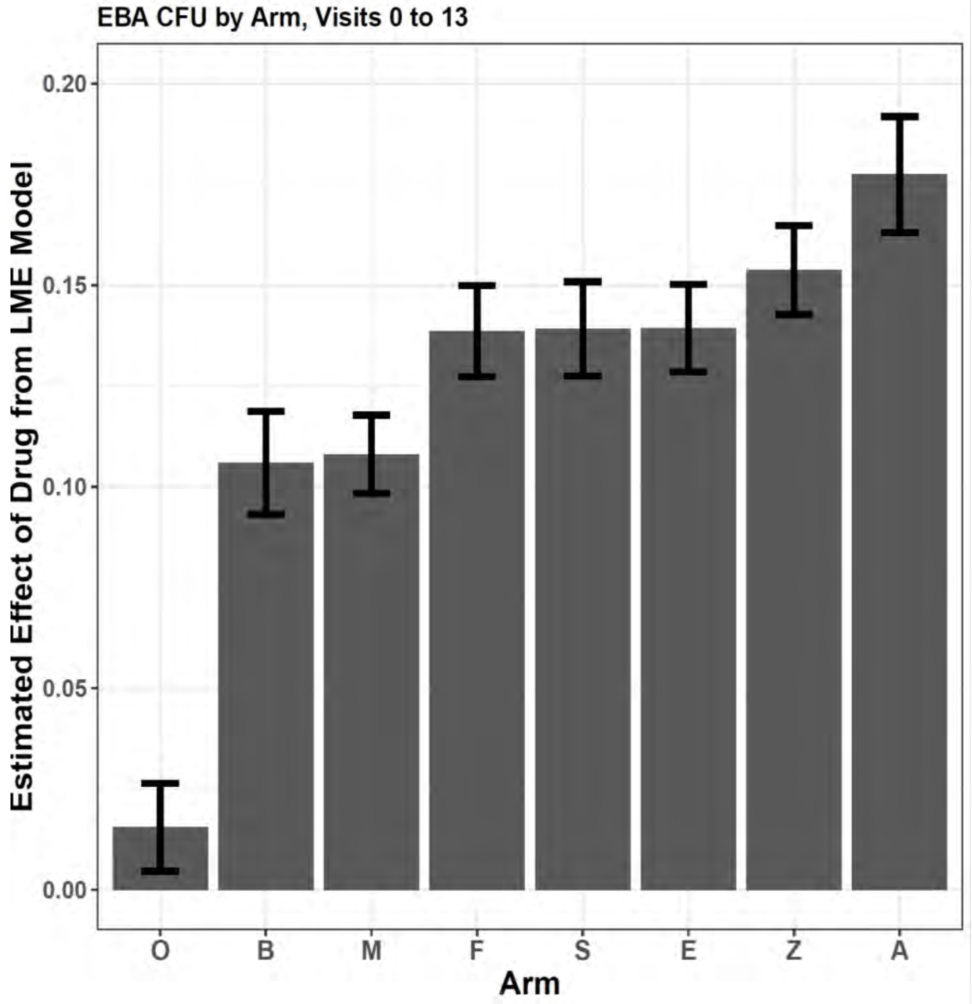
NIAID/NIH

Gerhard Walzl (Stellenbosch University)

Goal: Improve the ability to predict non-relapsing cure in TB patients in a short-duration trial amenable to combination chemotherapy.

Enrollment: December 2015 to September 2017



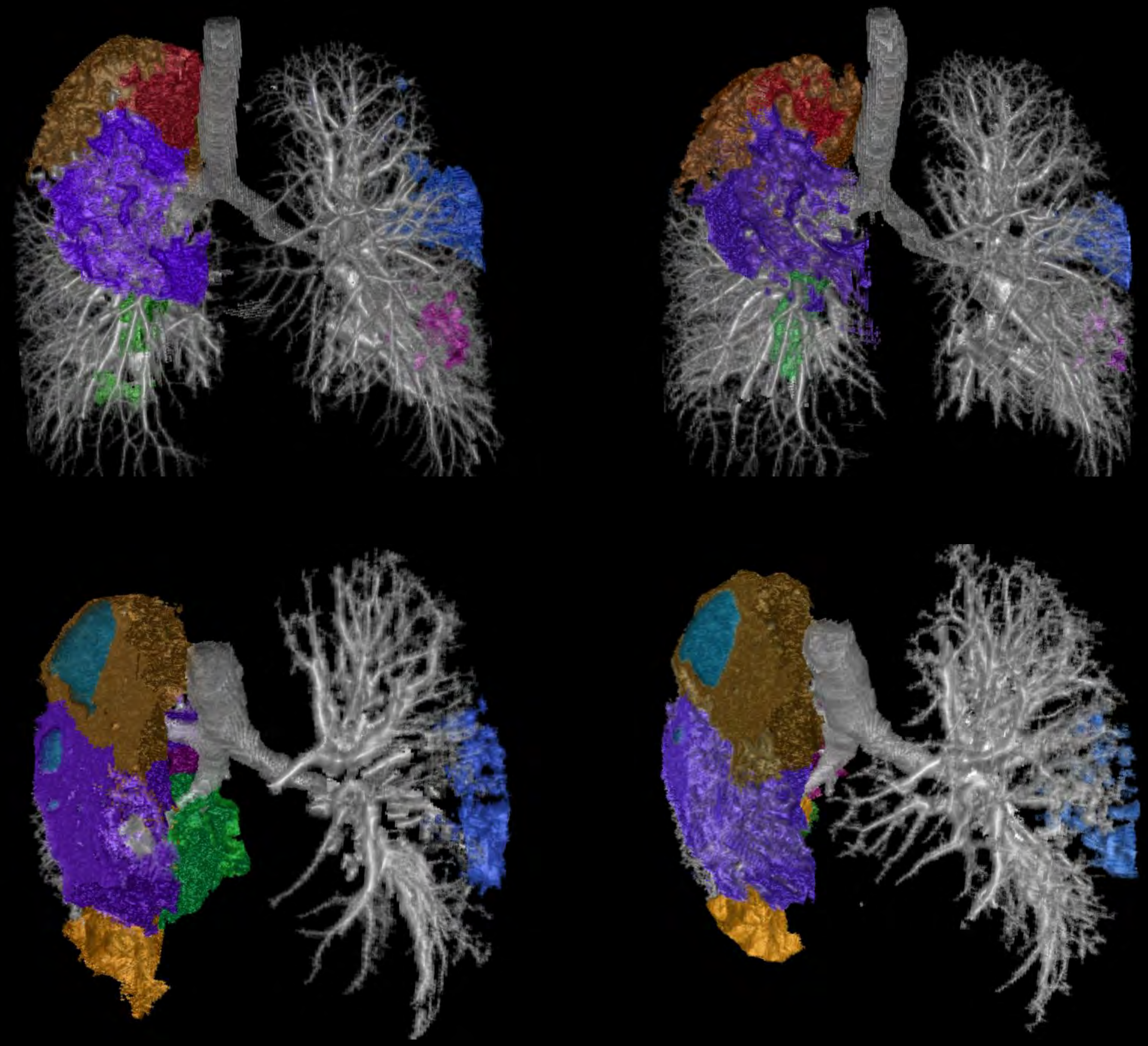


$EBA_{0\text{-}13}$ (mean daily $\log_{10}$ decline of CFU/mL sputum/day over 13 days of treatment) for the 8 blinded treatment arms, arbitrary arm designation

Pretreatment Baseline **After 14 days of Treatment**

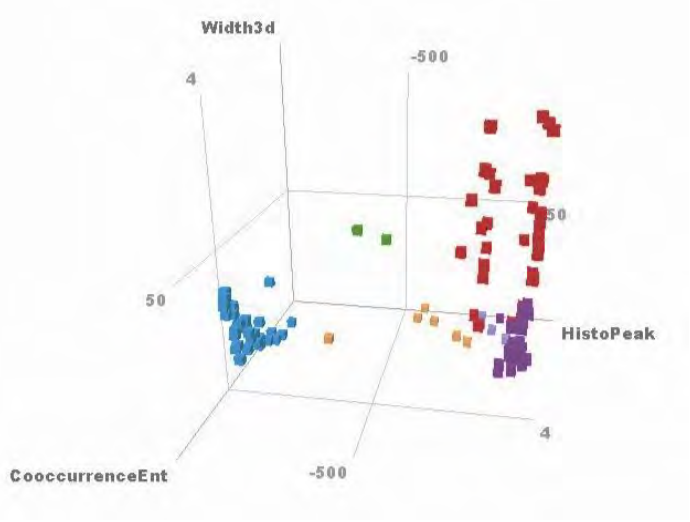
NG029: Improvement in all lesions

NG041: Heterogenous changes



NexGen EBA Analysis

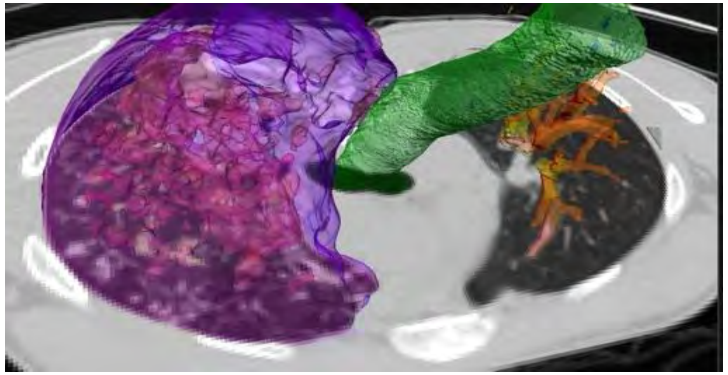
Derive PET/CT 1st and 2nd order statistics to categorize lesions into pharmacokinetically-relevant units (ongoing)

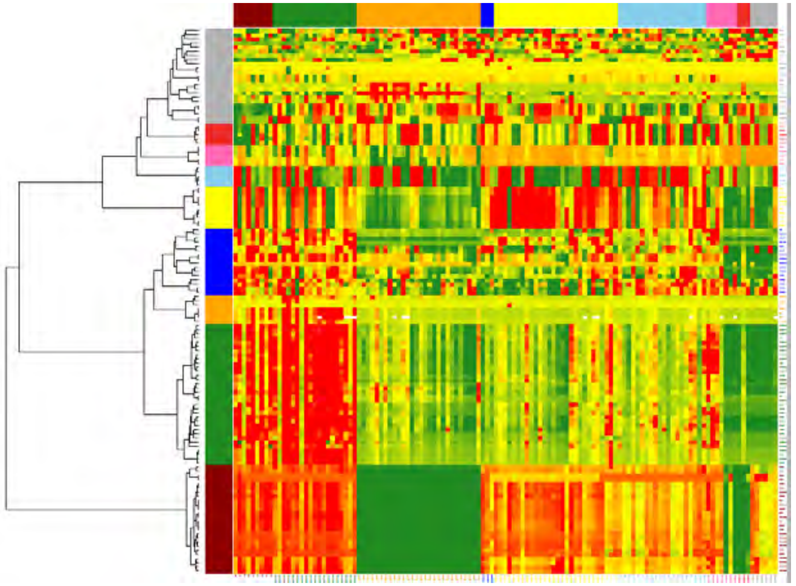


Extract lesions from all 320 study PET/CT scans:
Developing automated extraction method using machine learning from manual extractions (ongoing)

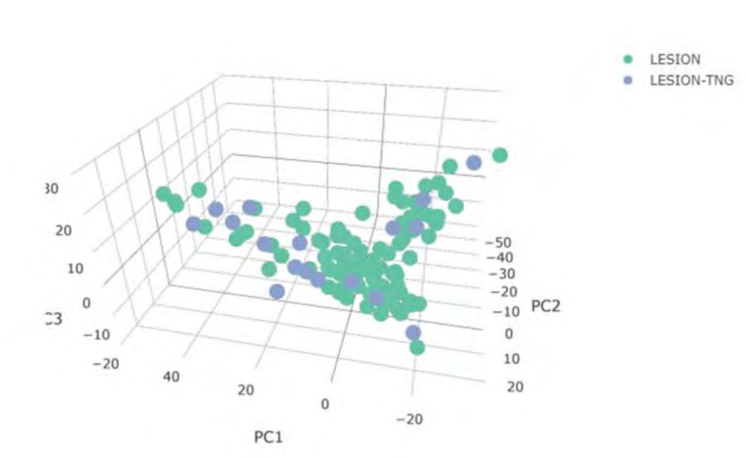
Apply these statistics to categorize all extracted lesions from participant scans

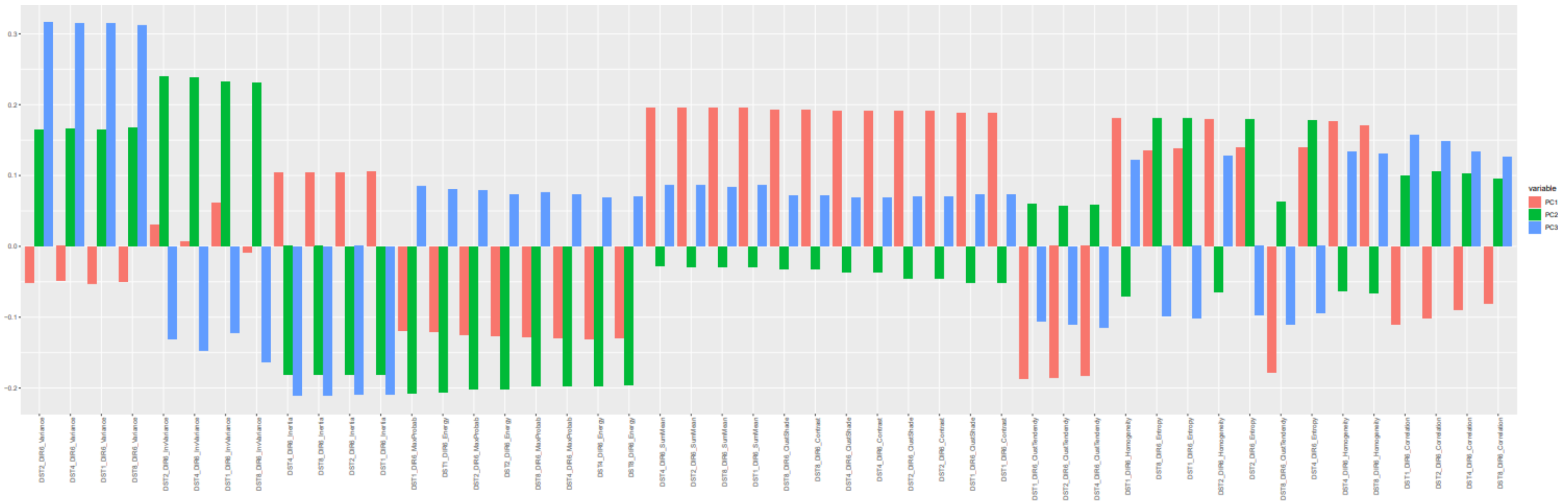
Measure delta signature of 14-day PET/CT changes across each lesion unit for each participant



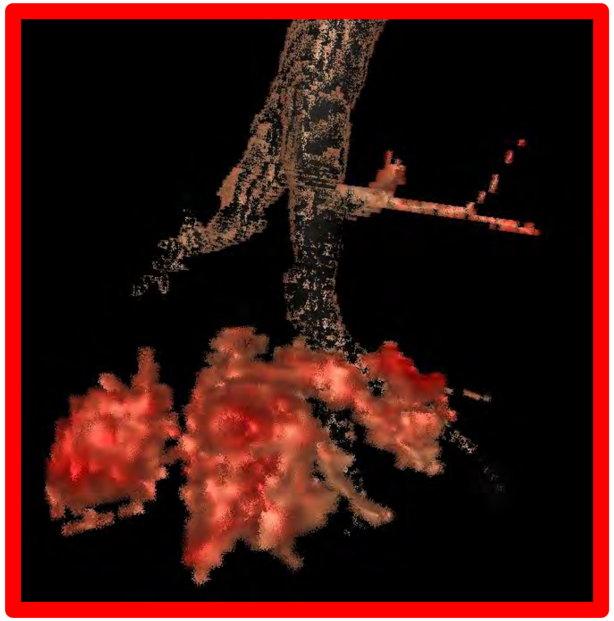


Prediction of all NexGen participant treatment arms based on these signatures
Comparison with microbiology and immunology data



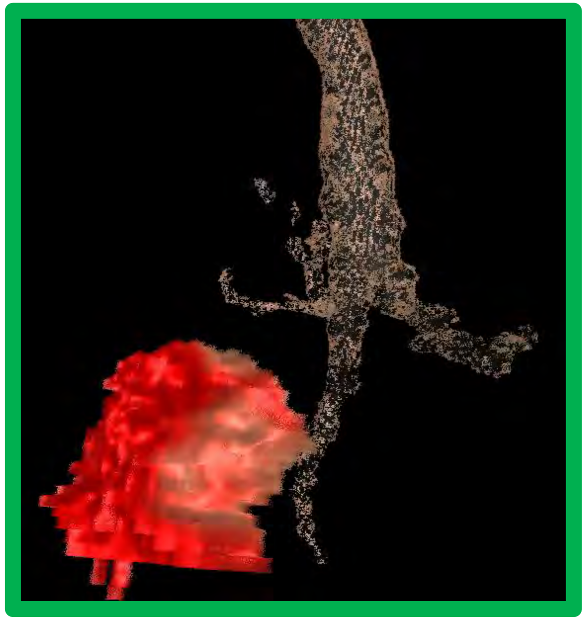


1) High in PC1



NG009_base_R6_lesion

2) High in PC2



NG039_base_L4_lesion_2

3) High in PC3

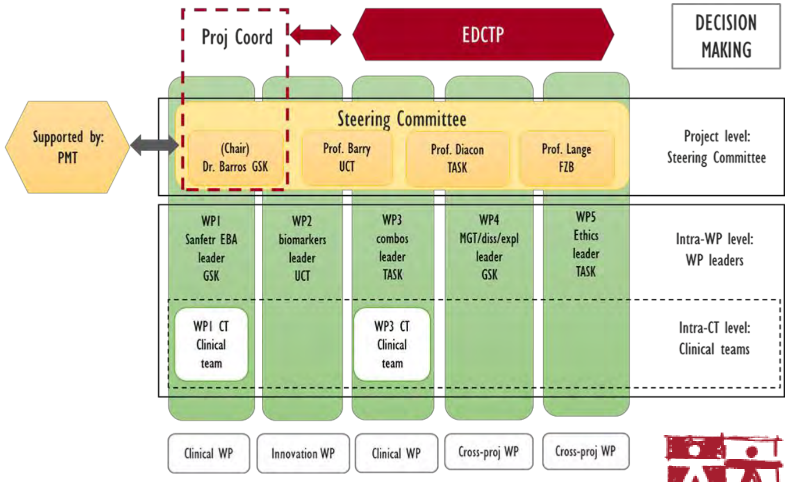
NG111_base_L1-5_lesion

4) Low in Everything

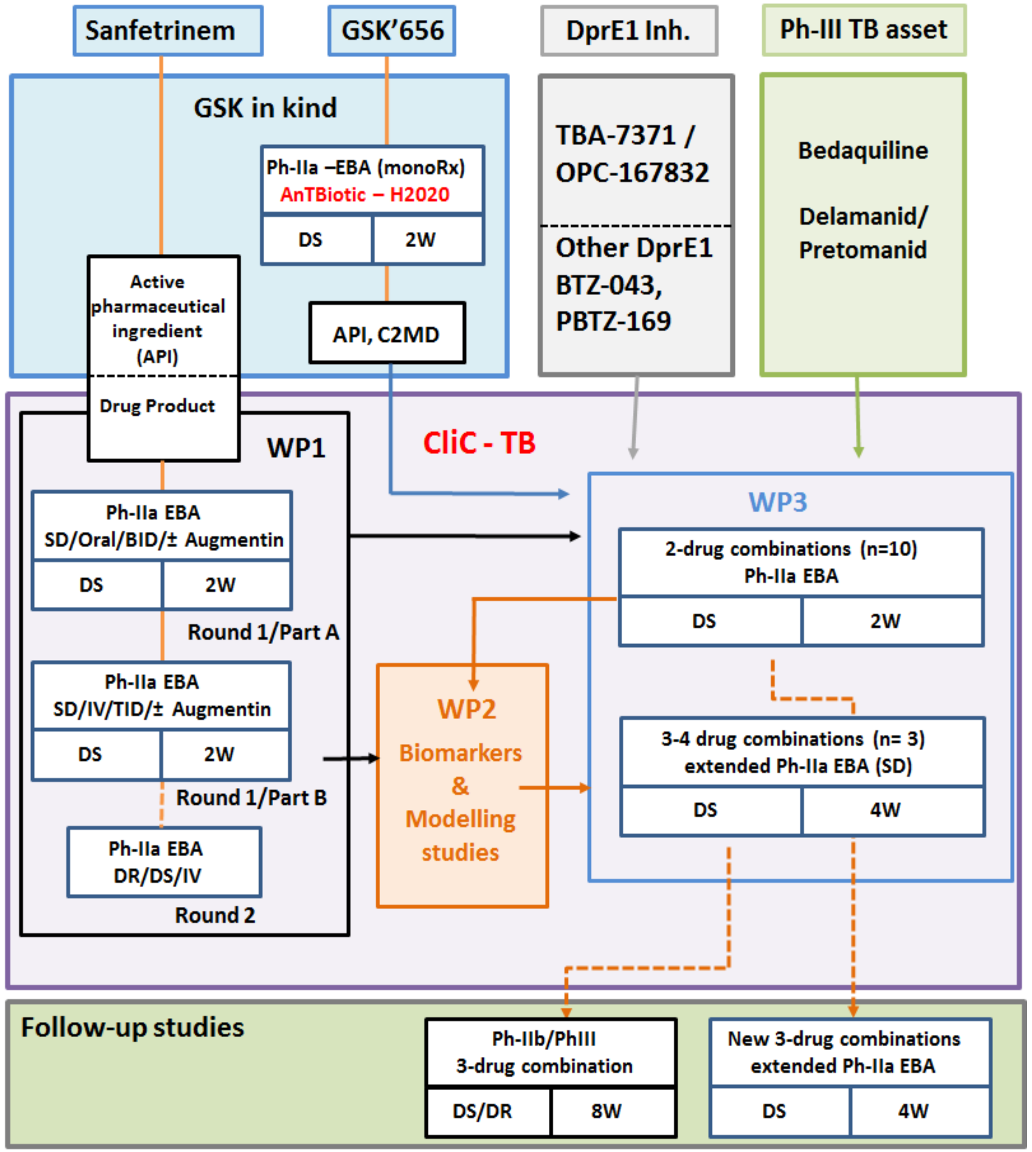
NG019_base_R4_R5_lesion

The next four years…

rewriting the rules for Phase 2 TB Rx studies



EDCTP



SD: Single dose; BID: Twice a day; TID: Three times a day ; EBA: Early bactericidal activity; IV: Intravenous; DR: Dose ranging; DS: Drug Sensitive; PoC: Proof of Concept; C2MD: Commitment to Medicine Development

Conclusions

- TB remains a persistent global health threat
- “Latent” TB is a wide spectrum with very different risks of progressing to active disease
- Preventing at-risk LTBI patients from developing disease using simple blood markers may soon be a reality
- “Personalized” TB therapy of appropriate drugs and treatment times should optimize use of the scarce resources available for TB control
- Improved drugs and clinical trial methodologies to combine them are being developed